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Vol. 31 No. 158 August, 1956

ARCHIVES OF DISEASE IN CHILDHOOD

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LONDON
BRITISH MEDICAL ASSOCIATION
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FREE DIETS IN THE TREATMENT OF DIABETIC CHILDREN

BY

CONSTANCE C. FORSYTH and W. W. PAYNE
From The Hospital for Sick Children, Great Ormond Street, London

(RECEIVED FOR PUBLICATION APRIL 9, 1956)

There is no doubt that the severity of diabetes mellitus can be modified by a restriction of the total calorie intake. This fact, established experimentally by Allen (1914, 1917), was the bulwark of treatment before the discovery of insulin, and low-calorie diets are still today the best method of treatment for obese diabetics. After the introduction of insulin, children survived long enough to show that the under-nutrition inherent in this method resulted in stunting of growth and, in many cases, enlargement of the liver. In view of this and the rarity of obesity in diabetic children, diets were progressively increased until at the present time it is generally accepted that they should be of normal calorie value (White, 1952). Children's activities are variable, their emotions labile and their appetites capricious. It is not surprising, therefore, that the next step towards normality, namely the use of free diets, was first reported from a children's clinic by Stolte (1931). Other paediatricians, including Lichtenstein (1938, 1945, 1949), Larsson, Lichtenstein and Ploman (1952) and Guest (1947, 1950), have since written in favour of this method.

The clinic for diabetic children at The Hospital for Sick Children, Great Ormond Street, was started in 1926. Initially, strictly weighed diets were used with a carbohydrate content of up to 100 grams daily. However, it soon became apparent that many of the children were hungry and that they were not growing well. The food intakes were gradually increased until normal in quantity and in 1936 free diets were tried for the first time. A few years later it was reported (Payne, 1939) that none of the children was more difficult to control on a free diet, and that in some control was actually easier. About this time the free diet method was adopted for the whole clinic and the availability of delayed-action insulins made control possible with one injection daily. The question arose, however, would these children in the long run show a higher incidence of complications than their contemporaries treated on strict diets? The following study of the long-term results on the method was undertaken to try to provide the answer.

It is impossible to include every diabetic treated since 1926, because at least a third of the patients were lost sight of during the war years. The paper deals only with those regularly attending and those who came for examination in response to our letter and were still on a free diet. One hundred patients were seen (a fortuitous total), 54 male and 46 female. In 41 cases the duration of diabetes exceeded 15 years and the others had been diabetic for between one and 15 years. Their ages ranged from 3 to 41 years and the longest period on a free diet was 18 years. The patients were interviewed and examined, particularly for evidence of retinal degeneration, and neurological, renal or vascular disturbances. Each had a chest radiograph, the blood sugar and cholesterol estimated and the urine examined for sugar, acetone, albumin, cells and casts. Mr. J. H. Doggart also examined the retinae in many cases and his opinion confirmed ours. For the few patients who could not visit his clinic this specialist corroboration was, however, not obtainable.

By the term 'free diet' we imply liberty rather than licence. Simple instructions are given to ensure the quality of the diet, and regular timing of meals is considered essential. Concentrated carbohydrates, such as table sugar, jam, chocolate and sweets, are restricted. It might conveniently be described as a Victorian diet providing unlimited quantities of plain fare. In practice, because the importance of avoiding insulin reactions is soon appreciated, cooperation is excellent with regard to the regularity of meals, and when the diets are analysed they are remarkably similar from day to day. It might be argued that the diet employed is not truly free; we agree. However, there is a real difference between such a simple diet and a strictly weighed diet demanding much care and intelligence from the parent and strict obedience from the child.

With regard to the standard of control to be set

in the early years of the clinic a stalwart attempt was made by using strict diets to keep the blood sugars normal and the urine sugar-free. In most children, however, this ideal was unattainable, so instead a more realistic target was adopted, namely, no symptoms either of thirst or polyuria or of insulin overdosage, normal growth and weight gain, no ketonuria, about half the urine tests done at home at varying times of day before meals to be sugar-free or virtually so, and the blood sugar level taken at the monthly visit to the clinic to be below 250 mg. %. The group of diabetics studied was divided into three categories according to the control actually achieved. Group A maintained the above standards of control for over three-quarters of their diabetic life, group B for between half and three-quarters of the time and group C for less than half of the time. Twenty-nine were in category A, 40 in category B and 31 in category C.

Following the introduction of delayed-action insulins, control by a single morning dose in suitable combination has been achieved in every patient. In the group of diabetics who have been under observation for more than 15 years, the dose of insulin steadily increased during childhood, reached its maximum at puberty and then fell to a fairly stable adult level. This typical pattern is illustrated for six of the boys and six girls in Figs. 1 and 2. Some showed a more even distribution of insulin over the years, but in only two did the final adult level exceed that at puberty. In the whole group the range of insulin requirement at 12 years was from 20 to 70 units, during puberty from 60 to 180 units and in adult life from 40 to 120 units. The steep rise in insulin dosage in adolescents was noted in a previous study of the use of 'free' diets (Forsyth, Kinnear and Dunlop, 1951), and most of the young people were changed on to restricted

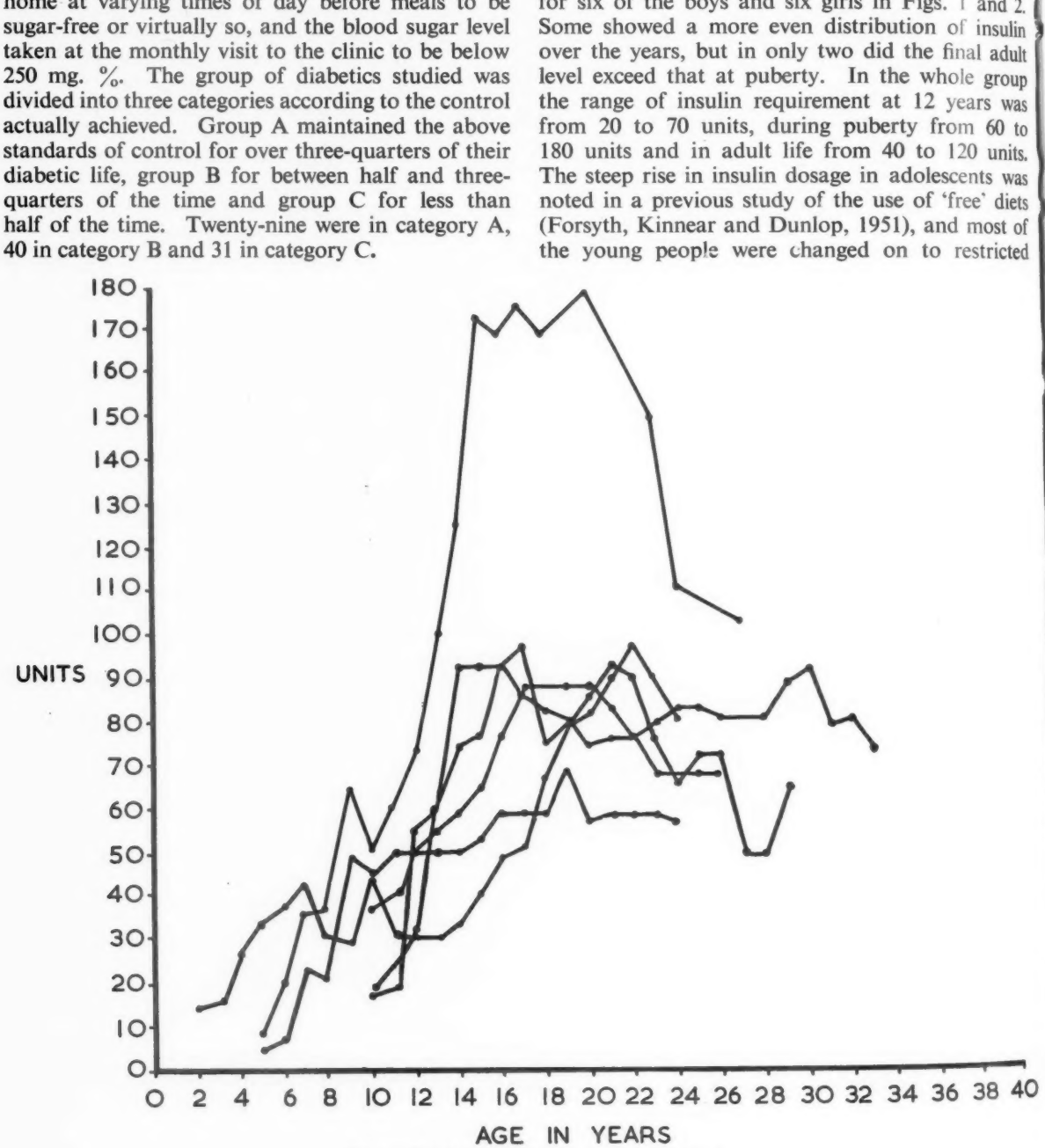

FIG. 1.—Relation of insulin dose to age in six boys.

diets as levels of insulin requirement above 80 units were then regarded as excessive. In the present group, over half the patients required more than 80 units for a few years at puberty but only one-fifth take more than 80 units as adults. The increase is not, as was supposed, due to a progressive impairment of carbohydrate tolerance, but is a phase in the natural history of the disease.

Reviewing the results of treatment of the hundred children on a free diet, we have found, except for short periods of loss of balance due usually to intercurrent infections, that all have remained entirely free from thirst, polyuria or ketosis. Insulin reactions have been mild and hypoglycaemic coma has been very rare. Detailed figures for the incidence of diabetic coma are not available for the group diabetic for more than 15 years, as they have not been under supervision at Great Ormond Street all the time. Of the 59 younger patients, five have had one coma, and only one child two episodes of coma, apart from those at the onset of diabetes. It must be admitted that timely advice on the telephone averted trouble on many occasions, and several children were saved from coma by prompt hospital treatment during acute infections accompanied by ketosis. The heights of those patients now over 20 years are given in Table 1 and it is evident that growth has been satisfactory. None of the adults has become obese but three girls

TABLE 1
HEIGHTS OF ADULT PATIENTS

Sex	4 ft. 11 in. to 5 ft. 2 in.	5 ft. 3 in. to 5 ft. 6 in.	5 ft. 7 in. to 5 ft. 10 in.	5 ft. 10 in. to 6 ft. 1 in.
Male (25)	0	4	18	3
Female (13)	6	7	0	0

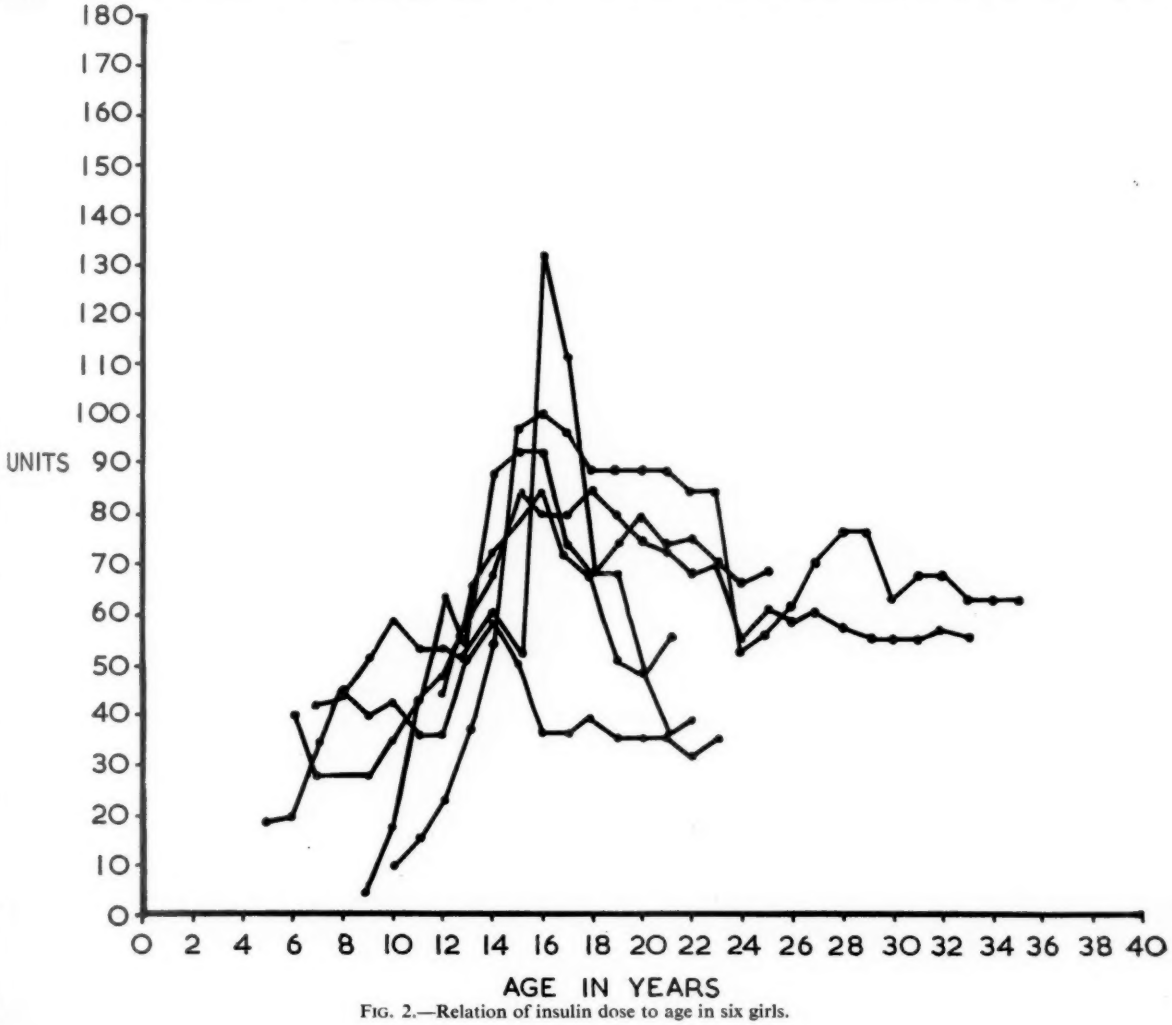

FIG. 2.—Relation of insulin dose to age in six girls.

showed this tendency at puberty. A short period of restricted food intake corrected this, a treatment one would give to any normal girl showing too rapid a weight gain at this age.

Hepatomegaly used to be frequent in diabetic children treated on restricted diets but was uncommon in our series. In three children under 4 years of age, who were clinically and biochemically well controlled, the liver could be felt one finger-breadth below the costal margin. In six children over 4 years of age, however, a similar finding was associated consistently with glycosuria. The liver was not palpable in any of the adults. Excluding the very youngest children, in whom a palpable liver may be quite normal for the age, this sign may be useful in assessing the efficiency of treatment.

The blood cholesterol levels were above 230 mg. % in five out of 57 of the younger group, diabetic for less than 15 years. One of these had retinitis, one had xanthomatosis lipoidica diabeticorum, two were passing much sugar at the time, but a girl of 4 appeared to be well controlled. In the older group, 30 were tested, and of these three showed high blood cholesterol levels. All three were of control category C and are included in Table 5 which shows those with severe complications. The blood cholesterol levels appear therefore to be more labile in children, but are nevertheless a useful additional guide to overall control in difficult cases.

As part of the follow-up, the chest was radiographed. The radiographs were negative in all of the patients diabetic for less than 15 years. There have been four instances of tuberculosis among those diabetic for longer than 15 years and one of these had both pulmonary and renal tuberculosis. He is now convalescent and the other three are well again and back at work (Table 2). Five patients who had had diabetes for more than 15 years have died and are not included in the hundred cases. One of these developed pulmonary tuberculosis and died after a lobectomy (Table 3). In all cases, the onset of tuberculosis was between 15 and 24 years of age, the period of maximal incidence of the disease in the general population. Since 1950, B.C.G. immunization has been carried out as a routine in the clinic and this may have modified the incidence in the more recent patients.

TABLE 2

FOUR CASES OF TUBERCULOSIS

Sex	Age at Onset (years)	Duration of Illness (years)	Outcome	Control before Onset
M	24	3	At work	C
M	19	5	At work	B
M	23	6	Convalescent	A
F	19	4	At work	C

None of the hundred patients complained of pains or paraesthesiae in the head, face, trunk or limbs, and neurological examination failed to reveal any instances of neuropathy. The vascular complications encountered were retinopathy, nephropathy and hypertension in that order of frequency. No cases of cerebral, coronary or peripheral vascular disease were detected clinically, but radiographs of the limb vessels were not taken. Of the five deaths in patients diabetic for more than 15 years, one was due to a cerebrovascular accident following pregnancy, one to renal failure following three pregnancies and one to renal failure in a single girl (Table 3).

Retinopathy was graded as follows: I, a few punctate haemorrhages only; II, several haemorrhages and some exudates; III, visual impairment with marked haemorrhages and exudates and occasionally venous changes; IV, certifiable as a blind person. The incidence and severity of retinitis in the hundred cases increased with the duration of the diabetes (Fig. 3). None of the blind patients had had diabetes for less than 20 years and two patients after 25 years of diabetes were free of retinitis. As there were no cases of retinitis in those diabetic for eight years or less, those 40 cases are omitted from Figs. 4 and 5. While it must be admitted that the daily insulin requirement does not reflect the clinical severity of diabetes, it was of interest to see if there was any correlation between retinitis and the dose of insulin (Fig. 4). No such relation emerged.

As at present the only factor which can be

TABLE 3

DEATHS IN THOSE SURVIVING 15 YEARS

Sex	Age at Death (years)	Duration (years)	Control	Retinitis	Nephropathy	Hypertension	Cause of Death
F	26	23	B	II	+	+	Stroke: 3 pregnancies
F	25	20	C	I	+	+	Nephropathy
F	29	20	C	III	+	+	Nephropathy: 1 pregnancy
F	19	17	C	—	—	—	Pulmonary T.B. Lobectomy
F	24	20	C	I	—	—	Status asthmaticus

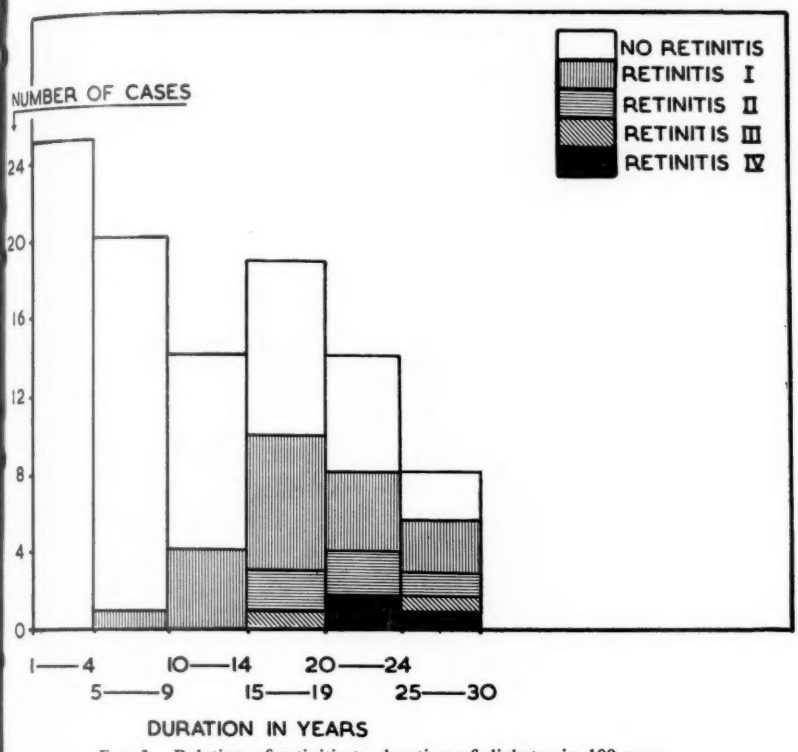

FIG. 3.—Relation of retinitis to duration of diabetes in 100 cases.

made of such a series of figures as occur in Table 4B. Using this method the two series show a difference significant between the 0·05 and 0·01 level of probability. It will be seen then, that the incidence of retinitis is in each age group higher in category C. (It is of interest that the 25 year+ group contains no cases in category C.) Thus only in those patients failing to satisfy the set standard of control for more than half of their period of diabetes was a rise in the incidence of retinitis noted. There was no difference between the two better controlled groups.

Nephropathy was diagnosed if there was a persistent albuminuria above 40 mg. % whether casts were seen microscopically or not. Hypertension was considered present when the diastolic blood pressure was above 90 mm. Hg, taking the point when the character of

influenced by the physician is the degree of control, the relation between the incidence of retinitis and degree of control is of importance. Examination of Fig. 5 reveals no difference in the incidence of the severer forms of retinitis in the three categories. There is, however, a suggestive increase in the total incidence of retinitis in group C. When the cases are arranged in relation to the duration of the disease, as well as their category (Table 4A), it will be seen that there is a very uneven distribution of cases of the different categories in the various age groups. By inspection it is evident that categories A and B show a similar incidence of retinitis. By adding groups A and B together it is possible to make a comparison with category C (4B). Armitage (1956) has devised a method enabling a statistical comparison to be

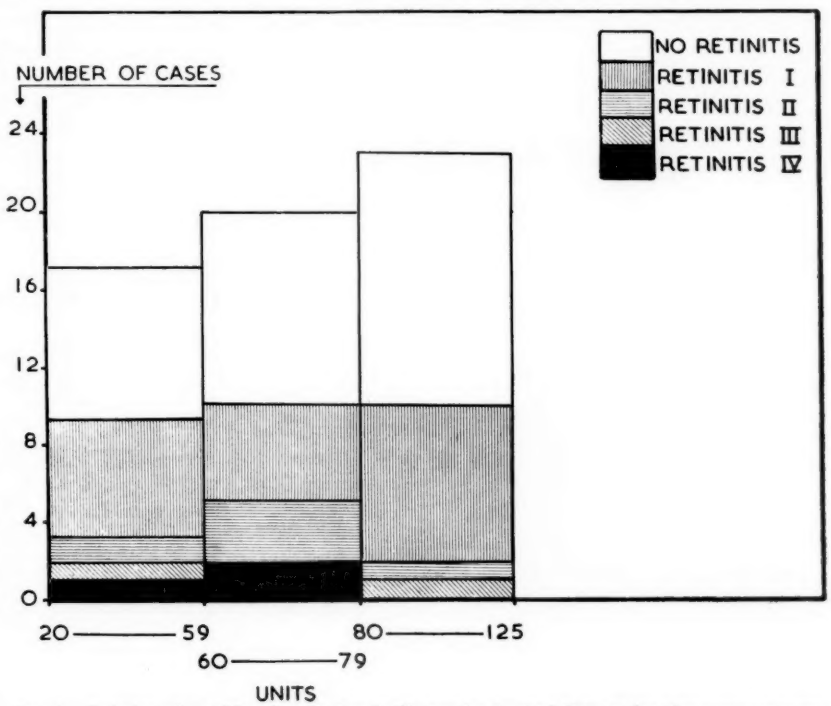

FIG. 4.—Relation of retinitis to insulin dose in 60 cases having had diabetes for nine years or more.

TABLE 4A AND 4B
RETINITIS AND CONTROL

4A

Category	Duration							
	9–14 Years		15–19 Years		20–24 Years		25–30 Years	
	Total	Retinitis	Total	Retinitis	Total	Retinitis	Total	Retinitis
A	2	0	6	3	2	1	4	3
B	10	2	5	1	5	2	4	3
C	7	3	8	6	7	5	0	0

4B

A+B	12	2	11	4	7	3	8	6
C	7	3	8	6	7	5	0	0

TABLE 5
CASES WITH VISUAL SYMPTOMS, NEPHROPATHY OR HYPERTENSION

Sex	Retinitis	Albuminuria (mg. %)	Blood Pressure (mm. Hg)	Duration (years)	Control
F	IV	70	175:98	24	A
M	IV	200	—	25	A
M	IV	300	—	22	C
F	III	95	—	15	C
M	III	—	—	25	B
M	II	400	160:110	22	B
M	II	80	150:96	24	B
M	II	550	—	26	A
M	II	70	—	19	C

the sounds altered as the diastolic pressure. In Table 5 the cases with visual symptoms, nephropathy and hypertension are summarized. It will be noted that albuminuria was present in all the blind and all the hypertensive patients. Of the nine patients, three fall into each of the categories A, B and C.

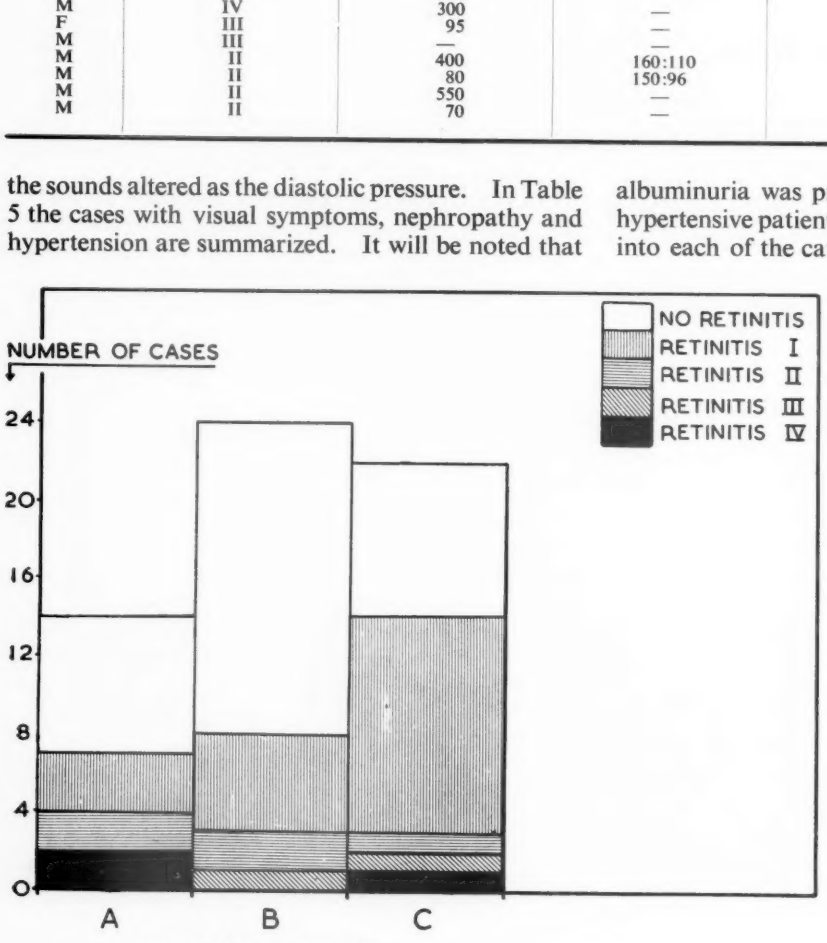

FIG. 5.—Relation of retinitis to control in 60 cases having had diabetes for nine years or more.

In contrast, the eight patients free of complications after 20 years of diabetes are listed in Table 6. The two with diabetes of over 25 years' duration were among those seen by Mr. Doggart. The woman had negative radiographs of the limb vessels and the young man is a successful long-distance racing cyclist. In this group of patients who have done well, there are two each of the A and C categories and four in the B category.

Discussion

Now that it is generally accepted that diets of full calorie value are essential for the normal growth and development of diabetic children, the only argument in favour of weighed diets is that by strictly controlling the food intake blood and urine sugars

TABLE 6

GROUP FREE FROM VASCULAR COMPLICATIONS AFTER 20 YEARS OR MORE

Sex	Age (years)	Duration (years)	Insulin (units)	Control
F	29	21	64	C
M	28	21	104	A
F	30	22	56	C
M	24	22	80	B
M	27	22	104	B
M	31	23	64	B
F	34	25	56	B
M	30	26	88	A

may be kept nearly normal. However, it is a mistaken assumption that a young diabetic is well balanced merely because he is keeping to his diet. Many other factors are involved in the regulation of blood sugar, such as the rate of absorption of the food taken and of the insulin from the injection site and the metabolic effects of exercise, environmental stresses or emotional upsets. The lives of young children are so variable that too fine an adjustment of diet and insulin leads to hypoglycaemic attacks which are psychologically detrimental and may even lead to permanent brain damage. Because of these practical problems, it is evident to those with experience in their treatment that absolute control by a strict diet is impossible in the vast majority of children.

The strongest argument against a weighed diet is the difficulty in persuading the patient to keep to it. This reluctance is by no means confined to young diabetics, and was particularly emphasized by Tunbridge (1953) in his lecture on the socio-medical aspects of diabetes mellitus. In a random sample of 103 diabetics attending the clinic at Leeds, only 16 were keeping to the diets, 44 were adhering partially to them and the remaining 43 were either uncooperative in the survey or their dietary habits were described as hopeless. Wilson (1951a), writing from Joslin's clinic about nephropathy in poorly controlled young diabetics, quotes a typical case as follows:

> 'The child and his parents are carefully instructed concerning the management of the newly discerned disease. Strict compliance with the instructions given about diet and insulin is maintained by the child's parents during the first few months. Gradually carelessness born of familiarity and monotony begins to creep into the management of the child's condition and as the years pass, gross neglect ensues, particularly beyond the age of 15 or 16 when the child has less parental supervision.'

These two illustrations are concerned with dietary excesses but in young children the opposite difficulty may also arise, namely refusal to eat, when there is an anxious insistence on the completion of a weighed meal. When such negativism is encountered it is often essential to allow freedom of choice if the child is to get an adequate calorie intake.

What are the results when a free diet is permitted? The standard of control set at the Great Ormond Street clinic has been achieved for more than half of their total diabetic life by 69 of 100 patients. This level of control has been clinically satisfactory on a short-term basis, as the incidence of hypoglycaemic and diabetic coma has been low, the children have been full of energy and have grown well and there has been no neuropathy and no greater an incidence of tuberculosis than would be expected.

In the Annual Report of the Ministry of Health for 1950, the notifications of respiratory tuberculosis between the ages of 15 and 24 years for the general population averaged 0·199%, that is 0·2% approximately. The incidence in groups of university students in Great Britain and Ireland according to Verney (1955) varied between 0·15% and 0·34%. Joslin (1952) quoted the incidence of tuberculosis as 12 times higher in diabetics than that of the general population and 20 times higher in adolescent diabetics. Boucot, Dillon, Cooper, Meier and Richardson (1952) reported the results of a survey of tuberculosis in the diabetics of Philadelphia; they used as controls a series of industrial workers balanced for age, sex and colour. The incidence of tuberculosis in diabetics was twice that of the control group, but considering only those aged between 15 and 24 years the incidence (6%) was between seven and eight times that of the corresponding controls. The incidence of tuberculosis in our group (4%) would appear therefore to agree with that in diabetics generally, and although the numbers are small it is notably lower than that quoted by Dunlop (1954) for the free diet clinic in Edinburgh (nine cases out of 50), this being his chief argument against free diets.

The long-term results are compared with those from other clinics for diabetic children in Table 7. The majority of these employed strict diets. Unfortunately, there are no British figures available for comparison. The number of children reported from clinics overseas is small, like our own, except in the case of White's large series. Nevertheless, it is evident that our incidence of retinitis, nephropathy and hypertension is no higher than in any of these clinics, and in some instances it is substantially lower. White's results are worse than those of the smaller clinics possibly because the patients were seen less frequently. Thus the use of practically free diets and the setting of a standard of control that has been attainable most of the time by the majority

TABLE 7
INCIDENCE OF COMPLICATIONS

	Duration (years)	Payne* (1955)	Larsson* (1952)	White (1952)	Jackson (1950)	Chute (1948)	Daeschner (1951)	Lundbaek (1953)
Number of Cases ..	15+	41	33		34	27	25	24
	15–19	19		?	24	14	10	15
	20+	22	—	702	10	13	15	9
Retinopathy	15+	59%	73%	—	68%	59%	80%	83%
	15–19	53%	—	50+%	58%	42%	70%	71%
	20+	64%	—	94%	90%	76%	93%	100%
Nephropathy	15+	20%	30%	—	6%	29%	32%	25%
	15–19	11%	—	25%	8%	21%	20%	27%
	20+	27%	—	57%	0%	38%	46%	22%
Hypertension	15+	7%	34%	—	6%	19%	36%	33%
	15–19	0%	—	25%	4%	7%	20%	27%
	20+	14%	—	50%	10%	31%	50%	44%

* On free diets.

of the children has not led to any comparative increase either in short-term or long-term complications.

What evidence has been put forward recently in favour of weighed diets? The largest series of young diabetics is that of Wilson *et al.* (1951a, 1951b, 1951c). The broad outlines of the division of his group into four categories of control is shown in Table 8 and the incidence of retinitis in those diabetic for more than 20 years in Table 9. It will be noted that although a weighed diet was prescribed, only 3% of the patients were on strictly weighed diets and that 85% were actually on free diets. This is a further illustration of the reluctance to adhere to strict diets. The group of poorly controlled patients is large and the incidence of retinitis in it is significantly higher statistically than in the other three groups taken together. None of this group exercised any commonsense caution about dieting and some were even irregular in their use of insulin. However, if the fairly well controlled group, who made some effort at controlling of their diabetes, is compared with the good and excellent cases taken together, the difference is very much less marked, and indeed, is not statistically significant. In Dunlop's survey of adults (1954), some details of which are given in Table 10, the poorly controlled group showed the

TABLE 9
WILSON'S RESULTS IN 103 YOUNG DIABETICS (DURATION 20 YEARS +)

Control	Number	Retinitis	Percentage
Excellent	4	1	25
Good	19	9	47
Fair	22	13	59
Poor	58	46	79

TABLE 10
DUNLOP'S RESULTS IN 167 DIABETIC ADULTS (DURATION 15 YEARS +)

Control	Number	Percentage	Retinitis	Percentage with Retinitis
Good ..	39	23	17	44
Fair ..	53	32	25	47
Poor ..	75	45	59	79

TABLE 8
WILSON'S RESULTS IN 247 YOUNG DIABETICS (DURATION 10 YEARS+)

	Number	Percentage	Assessment of Control
Excellent	7	3%	Weighed diets. Urine tests more than once every day sugar free before meals. Clinic visit at least once a year.
Good	30	12%	Measured diets. Urine tests once daily sugar free before meals. Clinic visit at least once a year.
Fair	51	21%	Urine tests once or twice a week sugar free before meals. Clinic visit at least every two years.
Poor	159	64%	Completely free diets. No routine urine tests. No routine clinic visits.

highest incidence of retinitis. The difference in the other two groups was insignificant. While our division of cases into A, B and C groups was not based upon exactly the same criteria as those of Wilson or Dunlop, it was nevertheless evident that again the C group, that is, those with poor control, showed a higher incidence of retinitis and that the A and B groups were virtually identical in this respect.

Examining why 31 patients should have fallen short of our standard of control for more than half of their diabetic lives, it became clear that, apart from a very few defaulters who would be classified with Wilson's poorly controlled group, the majority were poorly controlled because of a 'brittle' type of diabetes. A period of rigid dieting in hospital failed to improve the control when this was tried in some of the cases. Indeed, it appeared that the success or failure of control depended in many cases on variations in the disease itself rather than on adherence to dietetic instructions whether rigid or simple, as, in contrast to those brittle diabetics, there were the fortunate few who remained consistently in good control, yet who, except for their daily insulin, appeared to ignore their disease entirely.

The first aim of treatment should be to prevent as many children as possible from falling into the category of poor control, as this group undoubtedly shows a higher incidence of retinitis. Too rigorous a method, however, is likely to defeat its own object by provoking rebellion in the child and loss of confidence by the parents. Indeed, more may be gained than lost by using, instead of a strict regime, a simple diet of plain fare and a degree of control which the majority can reasonably hope to attain. A liberal method has resulted in excellent cooperation in the clinic at Great Ormond Street and we believe that successful treatment depends more upon faithful attendance for advice about insulin dosage and the tackling of day-to-day problems than upon the nature of the dietetic treatment advocated.

Summary

This survey of 100 diabetic children allowed 'free diets' deals with the short-term aspects and also with the incidence of degenerative complications in those who have reached adult life.

As the overall results of treatment have been as good as those obtained by clinics employing weighed diets and because of the psychological advantages and the better cooperation achieved, we believe that the use of a liberal diet will permit the best control in the greatest number of children.

We wish to thank Mr. J. H. Doggart for his assistance with the retina examinations.

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A CLINICAL AND BIOCHEMICAL STUDY OF GALACTOSAEMIA

A POSSIBLE EXPLANATION OF THE NATURE OF THE BIOCHEMICAL LESION

BY

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(RECEIVED FOR PUBLICATION JANUARY 27, 1956)

The clinical syndrome of galactosaemia is now well known and more than 40 cases have been carefully described in the literature (Bell, Lindsay and Watson, 1950; Bray, Isaac and Watkins, 1952; Donnell and Lann, 1951; Darling and Mortensen, 1954; Goldbloom and Brickman, 1946; Goldstein and Ennis, 1948; Göppert, 1917; Greenman and Rathbun, 1948; Hudson, Ireland, Ockenden and White-Jones, 1954; Johns, 1953; Maris and Valcke, 1953; Mason and Turner, 1935; Mellinkoff, Roth and MacLaggan, 1945; Mortensen and Søndergaard, 1954; Norman and Fashena, 1943; Reiter and Lasky, 1952; Townsend, Mason and Strong, 1951; Unshelm, 1934).

It is generally agreed that the disorder is the result of an inborn error of metabolism and it is thought that the condition is transmitted as a homozygous recessive gene (Holzel and Komrower, 1955). There is no definite knowledge of the aetiology of the condition but writers have suggested that there is an interference with the normal metabolic process:

$$\text{galactose} + \text{ATP} \xrightarrow{\text{galactokinase}} \text{galactose-1-phosphate} + \text{ADP}$$

uridyl transferase and

$$\text{galactose-1-phosphate} \xrightarrow{\text{galactowaldenase}} \text{glucose-1-phosphate}$$

and that the transformation of galactose-1-phosphate to glucose-1-phosphate is the site of the disturbance, as there is a deficiency of one of the two enzymes, uridyl transferase or galactowaldenase, which catalyse this reaction (Kalckar, Braganca and Munch-Petersen, 1953; Trucco, Caputto, Leloir and Mittelman, 1948). Galactose has always been implicated as the toxic agent, and the development of hepatomegaly, jaundice, cataract, mental retardtion, proteinuria, and, more recently, aminoaciduria, have been attributed to the damaging effect of this sugar on each of the organs concerned.

The objects of this communication are, first, to present two further cases of the condition with the results of routine investigations; next, to report the observations made on these children during milk or galactose feeding and, finally, to relate to these findings the biochemical studies of erythrocyte metabolism that have been made in the disease. In this way we shall endeavour to confirm the site of the interference and to indicate the nature of the metabolic upset.

Case Reports

Case 1. E.F., a girl, was born on June 7, 1951, of a normal delivery (birth weight 8 lb. 15 oz., breast fed). This was the sixth pregnancy, three had terminated with a miscarriage, one infant died aged 14 days, jaundiced, vomiting and with hepatomegaly: the coroner's necropsy report was 'fatty changes in the liver and liver failure'. The other child is alive and well but has an abnormal galactose tolerance and is in much better health when milk is omitted from his diet.

On the fifth day of life vomiting began; a marked loss of weight (1 lb.) was observed, also jaundice which increased in intensity during the next five days. On the tenth day the liver was palpable two fingers below the right costal margin. A radiograph of the chest was normal as was a barium swallow. The child was noticed to be drowsy and inactive although she took her feeds well. The urine on examination was found to contain protein and a reducing substance.

On the tenth day of life glucose saline feeds were started and given for three days; vomiting ceased and the child appeared less lethargic. On June 20 when breast feeding was restarted, the vomiting began again and the lethargy became more apparent. On June 21 the blood sugar (total) was noted to be 225 mg. per 100 ml. The reducing substance in the urine was found to be non-fermentable sugar. By this time the weight loss was 20 oz. and the liver had enlarged yet further to three fingers below the costal margin. The child was once again put on glucose saline feeds with 'casilan'. On June 23, when the child was 16 days old, the diagnosis of galactosaemia was made. On examination a small

superficial infection of the abdominal wall was noted where subcutaneous saline had been given; this required aureomycin therapy.

On June 27 the infant was transferred to the sick infants' ward of the hospital for further observation: she was still on the glucose saline and 'casilan' feeds and was gaining weight. On June 30 the blood sugar (total) was 108 mg. per 100 ml. On July 4 the milk feeds were restarted for the purposes of investigation. The following day the blood sugar (total) was noted to have increased to 202 mg. and following this the stools became loose, the vomiting recurred and an examination of the urine by chromatography confirmed the galactosuria and revealed a gross aminoaciduria.

During the rest of the month of July investigations of liver function, glucose and galactose tolerance tests, together with further examinations of the urine, were made. A careful examination of the fundi and media on July 23 did not reveal any abnormality.

Early in August she developed a low-grade pneumonia and a gastro-enteritis from which she recovered. She was then put on 'casilan' and dextrimaltose mixture which was thought to contain no lactose: this was subsequently found to be incorrect and explained the fact that the liver was still enlarging. On August 20 it was noted that on examination of the eyes there was an increased refractivity to light, and two days later cataracts were found and confirmed.

Bilateral cataracts in untreated case.

On August 24 a special mixture of 'farex', egg and dextrimaltose was started. There was no gain in weight for 10 days but by September 3 her general condition had improved considerably. There was no vomiting, the stools were more normal and the skin infection had improved: in addition examination of the urine did not reveal any aminoaciduria. Later in the month the strength of the feeds was adjusted and a steady improvement in general condition was noted. By the beginning of October there was a marked regression of the cataracts, the left eye being quite clear. The liver was only one and a half fingers palpable below the costal margin and the spleen tip could just be felt. It was noted that the child passed appreciable quantities of urine of low specific gravity with a maximum specific gravity 1011 which occurred 11 hours after a feed. On November 28 the glucose tolerance test was repeated while on the lactose-free diet, and was shown to be normal. Early in December liver function tests were found to be normal and the intelligence of the child, as tested by the Gesell technique, did not seem to be impaired. In addition the fundi were quite normal and there was no abnormality of the media of the eyes.

On December 8, aged 6 months, she returned home weighing 11 lb. 3 oz.

She was readmitted on February 25, 1952, for further investigation. By this time she weighed 14 lb. 3 oz., the urine contained no reducing substances and the amino-acid chromatogram was normal. In addition the glucose tolerance test showed no abnormality. The liver was just palpable, the spleen was not felt, the eyes were normal. Her general condition was excellent.

Her urine output averaged 23 oz. a day for two days with a low specific gravity of 1002. On March 3 a half-cream National dried milk feed was begun. Reducing substances were discovered in the urine after two days and protein after four days; it was noted that the aminoaciduria began after four or five days. There was, interestingly enough, a reduction in the urinary output. By the eighth day there was a gross aminoaciduria and the liver had enlarged two fingers below the costal margin.

She was discharged home on March 12 when the special diet was started again. She has since made steady progress; her weight in March, 1953, was 22½ lb., her general condition excellent and her intelligence normal. She was walking and talking, there was no hepato-splenomegaly but she was still intolerant of milk and her galactose tolerance was grossly abnormal.

Investigations made at this time showed that an aminoaciduria was produced when she was given milk feeds.

Further observations (*vide infra*) were made in October, 1954; in July, 1955 (aged 4 years), the results of a clinical examination were perfectly normal and intelligence testing suggested that her mental development was unimpaired.

Routine Investigations in Case 1

The galactose tolerance test and the glucose tolerance test are described in the section on carbohydrate studies.

LIVER FUNCTION TESTS

	* 21.6.51	* 23.7.51	4.9.51	4.12.51	* 12.3.52
Thymol-turbidity (units)	2·5	2·1	1·8	1·7	1·7
Serum alkaline phosphatase (units per 100 ml.) ..	17	40	23	26	50
Serum bilirubin (mg. per 100 ml.)		1·6	0·4	0·2	1·8
Serum albumin (mg. %)		3·3	3·6	4·0	3·4
Serum globulin (mg. %)		2·0	2·1	2·3	2·0

* Diet contained lactose or galactose.

A blood count on August 10, 1951, gave: red cells 3·8 m., Hb 72%, leucocytes 8,800 (polymorphs 38%. lymphocytes 62%).

Renal function is described in the section on renal investigations.

Radiographs of the hands and wrists, skull and long bones (May 27, 1952) showed that no evidence of any

deficiency disease could be detected in the skull or in the long bones: in the right hand there was a distinct suspicion of a cystic area in the neck of the third metacarpal, and possibly in the neck of the fourth.

Nothing abnormal was detected in radiographs of the hands, wrists and chest on January 24, 1953.

Case 2. A.K., a girl, was born on December 11, 1953, of a normal delivery (birth weight 7 lb. 10 oz.). She was admitted under the care of Dr. Margaret Egan on the 14th day of life because of a reluctance to feed, persistent vomiting and failure to thrive.

She was the first child, and there was no consanguinity; one distant relative had diabetes.

On examination the child was wasted and deeply jaundiced; the liver was enlarged, extending to below the umbilicus, the spleen was not palpable. There was a purulent vaginal discharge.

The immediate relevant laboratory data were as follows: serum bilirubin 14·2 mg. per 100 ml., Coombs test (direct) negative; Wassermann reaction negative. A blood film was normal without spherocytosis; haemoglobin 130%. The urine contained protein and a reducing substance, shown by chromatography to be galactose.

The condition of the infant deteriorated and intravenous plasma with N/5 saline and 5% dextrose was given: on January 2, 1954 (22nd day of life) the diagnosis of galactosaemia was made and a modified diet was instituted. This consisted of feeds of 5% glucose and 'casilan' and was given for several days; the child's general condition did not improve to any appreciable extent and early bilateral central cataracts were noted for the first time. In addition a reducing substance was still to be found in the urine.

The signs and symptoms regressed when the lactose-free diet was introduced and her general condition had improved greatly by the time she was transferred on February 12 to St. Mary's Hospitals for further studies.

On admission she weighed 8 lb. 5 oz., her general condition was fair, the liver was enlarged two fingers below the costal margin but the spleen was not felt. A small cataract was still to be seen in the right eye; the left eye was completely clear. Investigations were began and the child made a slow but steady improvement. By March 15 the cataract in the right eye had gone and her motor development seemed to be perfectly normal. The liver was still palpable and she had one large fluid stool daily. She continued in good health until April 12 (five days after the completion of an eight-day régime of milk feeding) when she had a sharp attack of gastro-enteritis which demanded intravenous plasma, 10% dextrose and Hartmann's solution. She was given streptomycin, 4 × 125 mg., and recovered quickly. Following this her progress was excellent and she returned home on May 4.

She has been under constant supervision since that date and has had two further admissions to hospital for additional observations.

She was seen on January 14, 1955 (aged 13 months), and her weight was 18½ lb. She walked and talked a little, was very active and happy and had a perfectly normal intelligence. Her general condition was good, the liver was not palpable, there was no evidence of cataracts and the urine examination revealed no abnormality.

She was also seen in July, 1955, a healthy, happy child weighing 23 lb. Her intelligence was tested at the time and found to be perfectly normal.

Routine Investigations of Case 2

The galactose tolerance test and glucose tolerance test are described in the sections on carbohydrate studies.

In February, 1954, thymol turbidity was 6 units, serum alkaline phosphatase 23 units/100 ml., serum albumin 3·74 mg. %, and serum globulin 2·61 mg. %. (The child was not fully treated at this stage.)

Full blood counts were all within normal limits and the clotting time, off milk, was 3 minutes, and on milk it was 5 minutes.

A radiograph of the skeleton was normal and the renal function tests will be discussed in the section on urinary investigations.

Carbohydrate Studies

We now present the results of investigations carried out on the two children while on milk or galactose feeding. The observations were made on five separate occasions (see Appendix).

Glucose Tolerance Tests. Glucose tolerance tests were carried out on both children whilst they were on milk-free diets (Table 1). Both curves are somewhat flat but the amount of glucose given was relatively small (1·25 g. per kg.).

TABLE 1
GLUCOSE TOLERANCE TESTS

E.F. November 28, 1951, Given 5·5 g. Glucose (mg. per 100 ml.)		A.K. February, 1954, Given 5·5 g. Glucose (mg. per 100 ml.)
Fasting	65	80
30 min.	95	95
60 ,,	83	95
90 ,,	79	85
120 ,,	73	60

Galactose Tolerance Tests. These were abnormal with galactose indices above 600 (Fig. 1). In one child (E.F.) the test was repeated at 2 years of age and showed no change for the better.

The depression of the blood glucose levels reported by several authors (Hudson *et al.*, 1954; Townsend *et al.*, 1951) was noted and on two occasions pallor, sighing respirations and sweating were observed during the investigation; in one case (A.K.) we are certain that the symptoms were related to a hypoglucosaemia (18 mg. per 100 ml.).

In the child A.K. the galactose tolerance test was repeated with the administration of 7 g. glucose simultaneously with the galactose (Fig. 2). There was a definite modification of the curve (Bruck and Rapoport, 1945; Greenman and Rathbun, 1948; Wagner, 1943) with a slower rise of galactose to a considerably lower level, and a smaller quantity of galactose was excreted

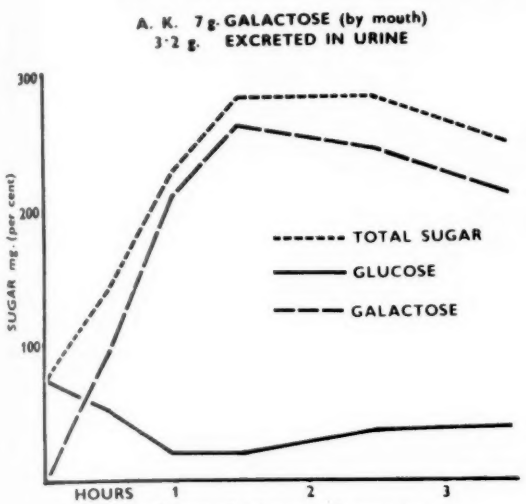

FIG. 1.—Curves of galactose tolerance test.

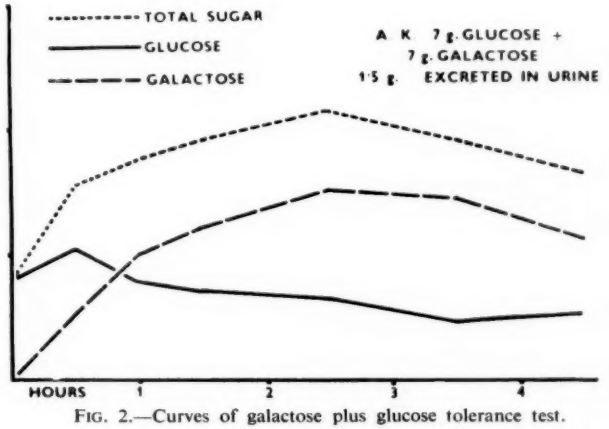

FIG. 2.—Curves of galactose plus glucose tolerance test.

in the urine. This probably was due to a slower absorption of galactose from the intestine in the presence of glucose (Cori, 1926), possibly permitting an improved utilization of galactose by the tissues.

Chromatography of Blood Sugars. On a galactose-free diet only glucose was detected but on a milk diet both glucose and galactose were found. No lactose was found in 0·15 ml. blood, indicating that the maximum blood lactose level was below 16 mg. per 100 ml.

Blood Glucose and Galactose Levels. No galactose was found either in the blood or in the urine when the children were on galactose-free diets, and the blood glucose levels, determined immediately before and two hours after feeds, ranged between 92 mg. and 113 mg. per 100 ml. blood.

An appreciable quantity of blood galactose was detected after 24 hours of milk feeding and the level continued to rise throughout the eight days of the observation (Table 2).

TABLE 2
BLOOD GLUCOSE AND GALACTOSE LEVELS IN A.K. ON A MILK DIET

Day	Date	Time	Glucose (mg./100 ml.)	Galactose (mg./100 ml.)
1	31/3	11 a.m.	97	56
	,,	4 p.m.	73	61
2	1/4	4 p.m.	89	47
3	2/4	10 a.m.	63	97
	,,	4 p.m.	76	91
6	5/4	10 a.m.	43	152
	,,	4 p.m.	61	162
7	6/4	10 a.m.	68	113
10	9/4	10 a.m.	100	Nil two days after cessation of milk

Blood collected by heel prick.
(a) at 10 a.m.—just before 10 o'clock feed.
(b) at 4 p.m.—two hours after last feed.

The blood glucose levels, although appreciably lower, were not as low as other writers have reported. This was probably due to the addition of glucose (1 drachm (3·9 g.) to 4 oz. feed) to the milk feeds.

Once the milk feeding ceased, the blood galactose levels dropped rapidly and in one observation the level was zero 15 hours after the termination of a 10-day spell of galactose feeding, while in the other child galactose was not detected either in the blood or urine 24 hours after the milk diet had ceased.

The amounts of galactose excreted in the urine are listed below (Table 3). There is a steady rise in the excretion of the hexose until the end of the milk or galactose feeding whereafter there is a rapid fall in the amount of sugar in the urine. In one case no galactose was found in the urine during the second day after the test period. In both cases the blood galactose level returned to zero within 24 hours.

TABLE 3
GALACTOSE INTAKE AND EXCRETION IN A.K. DURING EIGHT DAYS ON A MILK DIET

Day	Date	Galactose (g.) Taken by 3 p.m.	Galactose (g.) Excreted by 3 p.m.	% Excreted	% Retained
1	30–31/3	15·2	4·6	30	70
2	31–1/4	18·9	3·7	20	80
3	1–2	17·7	2·7	15	85
4	2–3	15·9	4·5	28	72
5	3–4	16·5	6·6	40	60
6	4–5	17·1	6·4	37	63
7	5–6	17·7	6·5	37	63
8	6–7	15·2	9·6	63	37
9	7–8	Nil			
10	8–9	Nil	Nil	—	—

Assuming that the lactose is completely absorbed from the gut it is possible to assess the proportion of galactose retained or utilized by the patient (Table 3). It is immediately obvious that an appreciable proportion of the hexose is metabolized and this observation supports the statements of Bruck and Rapoport (1944) and Cusworth, Dent and Flynn (1955).

The high value on day 8 may be due to the timing of micturition in relation to the start and finish of the day's collection. The volume of urine passed on day 8

The amino-acid spots are drawn in the form of circles, the relative sizes of the circles giving some indication of the strength of ninhydrin colour and hence of the quantity of each amino-acid. The urine has been applied at the right-hand bottom corner. Phenol has been run as first solvent from right to left followed by collidine in an upward direction.

Fig. 3

Identification of the spots.

1. Cysteic acid. 2. Aspartic acid. 3. Glutamic acid. 4. Serine. 5. Glycine. 6. Threonine. 7. Alanine. 8. Glutamine. 9. Tyrosine. 10. Phenylalanine. 11. Leucine. 12. Valine. 13. Alpha-amino-n-butyric acid. 14. Methionine. 15. Histidine. 16. Citrulline. 17. Beta-amino-isobutyric acid. 18. Methylhistidine. 19. Lysine. 20. Taurine.

FIG. 3.—Urine amino-acid chromatogram in an untreated case of galactosaemia.

Fig. 4

FIG. 4.—Urine amino-acid chromatogram before galactose feeding in A.K. aged 3 years 4 months.

Fig. 5

FIG. 5.—Urine amino-acid chromatogram after four days galactose feeding: 24 g. a day added to the diet.

Fig. 6

FIG. 6.—Urine amino-acid chromatogram after seven days of galactose feeding: 24 g. a day added to the diet.

Fig. 7

FIG. 7.—Urine amino-acid chromatogram two months after return to milk-free diet.

(413 ml.) is greater than that on day 7 (315 ml.) and the previous daily average (326 ml.); hence we would expect more galactose to be passed.

Results of Urinary Investigations

The presence of a gross aminoaciduria in untreated cases of galactosaemia was first described in 1952 (Holzel, Komrower and Wilson), and several workers have confirmed these observations (Bickel and Hickmans, 1952; Bickel and Thursby-Pelham, 1954; Darling and Mortensen, 1954; Cusworth *et al.*, 1955; Hsia, Hsia, Green, Kay and Gellis, 1954). The amino-acid pattern has been essentially similar in all cases, with a predominance of the neutral simple aliphatic chain type, i.e., serine, glycine, alanine, threonine, glutamine and valine; in addition phenylalanine, lysine, cystine, glutamic acid, methylhistidine, tyrosine, and amino-iso-butyric acids have been detected in the urine of these infants (Fig. 3).

In both our cases it was possible to restore the urine amino-acid pattern to normal by offering the infant a lactose- or galactose-free diet, and also to reproduce the abnormal picture by introducing adequate amounts of milk or galactose into the feed. In one child (E.F.) this observation was repeated at the age of 3 years 4 months after an interval of two years (Figs. 4, 5, 6, 7).

The serial urine chromatograms and daily estimations of total urinary amino-nitrogen show that the outpouring of amino-acids begins on the fifth or sixth day of milk or galactose feeding and continues to increase up to the tenth day (no investigations have continued longer than this). The amino-aciduria declines quickly once the milk feeding ceases and the chromatogram picture takes approximately one week to return to normal (Fig. 8).

The daily urine total nitrogen value remains fairly constant as does the urine urea-nitrogen (Fig. 9); there is, however, a marked increase in the daily urine amino-nitrogen output during the feeding experiment.

A small number of plasma and blood α amino-nitrogen levels were estimated (Table 4); some have been normal

TABLE 4

BLOOD AND PLASMA AMINO-NITROGEN LEVELS

E.F. aged 6 months	Plasma Amino-nitrogen (mg. per 100 ml.)	Urine
Milk diet	3·8	Chromatogram very abnormal
aged 18 months (Milk-free diet)	5·5	Chromatogram normal
A.K. aged 3 months	**Blood Amino-nitrogen (mg. per 100 ml.)**	**Urine Amino-nitrogen**
(Milk-free diet)	9·1	32·1 mg. per 24 hours
(Milk diet for eight days)	10·1	520 mg. per 24 hours

We are indebted to Dr. C. E. Dent for the estimations of plasma α amino-nitrogen (method of Hamilton and Van Slyke, 1943).

but the blood levels estimated by the method of Frame, Russell and Wilhelmi (1943), which is not completely specific, were slightly raised. There is, however, final evidence (Hsia *et al.*, 1954; Cusworth *et al.*, 1955) to confirm the original suggestion (Komrower, 1953) that there is a renal amino-aciduria with normal plasma levels of α amino-nitrogen.

Proteinuria. This has been reported in all the early cases of galactosaemia described in the literature; in our observations it appeared without fail within 48 hours of milk or galactose feeding and increased steadily until the end of the régime, substantial quantities of protein being excreted. The proteinuria diminished rapidly following the cessation of the milk feeding and disappeared after four or five days (Fig. 10). Electrophoresis of these urines revealed the normal range of plasma proteins.

Blood Urea. Blood urea determinations were made on three occasions and in each instance the result was within normal limits (24 mg.-33 mg. per 100 ml. blood).

Specific Gravity. The specific gravity of the urines varied considerably and revealed an ability to dilute and concentrate normally (Child E. F., fasting, sp. gr. 1018 and 1011; one hour after a feed sp. gr. 1001. We only obtained random determinations on child A.K. and the range was sp. gr. 1001-1013). The daily excretion of creatinine was not affected by the giving of milk or galactose (Fig. 11).

Excretion of Sodium, Potassium and Salt. A single study was made on child A.K. on November 19, 1954. The same daily diet was given all through the period of observation and she did not vomit on any of the three collection days; all the diet was taken each day. The child's motions were normal, apart from three loose stools during the last two hours of the final day.

There does not appear to be any significant alteration in the urinary excretion of sodium or potassium during the feeding experiment (Table 5).

TABLE 5

URINARY EXCRETION OF POTASSIUM, SODIUM AND SALT DURING A FEEDING EXPERIMENT USING GALACTOSE IN A.K. AGED 1 YEAR

Day	24 hour Urine Volume (ml.)	K (g.)	Na (g.)	NaCl (g.)
0	510	0·66	1·7	3·2
5	451	0·5	1·5	1·8
10	515	0·52	1·9	2·8

Acidification of the Urine. Both children showed a normal renal mechanism of acidification when given ammonium chloride (Table 6).

All these investigations suggest that there is no established renal damage in cases of galactosaemia that are treated efficiently and in these two children, who are respectively 4 years and 20 months old, there is no clinical evidence of renal impairment nor do the usual laboratory tests suggest it.

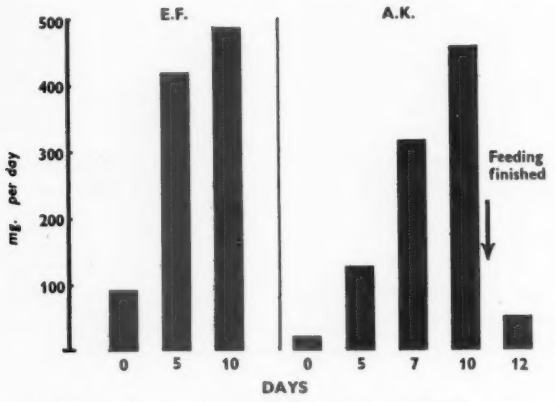

FIG. 8.—Daily urinary amino-nitrogen levels during feeding observations with galactose (E.F.) and milk (A.K.).

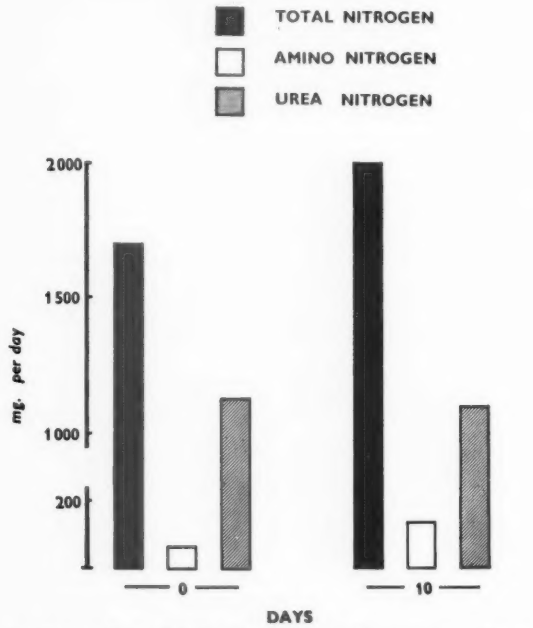

FIG. 9.—Comparison of daily urinary total nitrogen, urea-nitrogen and amino-nitrogen during a period of administration of galactose in the diet (E.F.).

TABLE 6
ACIDIFICATION OF URINE ON MILK-FREE AND GALACTOSE DIETS

	Urine *p*H			
E.F. Test dose NH4Cl. 2 g.	Before Test Dose	After 1 Hour	After 2 Hours	After 3 Hours
Milk-free diet ..	6·4	5·4	5·6	5·2
Galactose diet (20 g. daily) ..	6·7		5·6	5·4
A.K. Test dose NH4Cl. 0·5 g. Milk-free diet ..	6·4	5·4	5·3	5·2

Acidosis. Although acidosis is included among the results of routine investigations by some workers, its presence was not commented upon until Arthurton and Meade (1954) suggested that it might be of renal origin. In the case described by Bruck and Rapoport (1945) a hyperchloraemic acidosis was noted but not discussed further.

An acidosis was noted in the elder child (E.F.) when she was 12 months of age and in the second child (A.K.) when she was 3 months old. The blood bicarbonate level returned to normal when a milk- or galactose-free diet was resumed (see Table 7). The urine *p*H determinations suggested the possibility of a renal acidosis similar to that found in hyperchloraemic renal acidosis, and we repeated the investigations at 3 years 4 months (E.F.) and 12 months (A.K.) hoping that this point would be clarified.

The results were unsatisfactory as we were unable to reproduce the acidosis in the 10-day period of galactose feeding to which we were limited. (We considered that any longer period would be unsafe.)

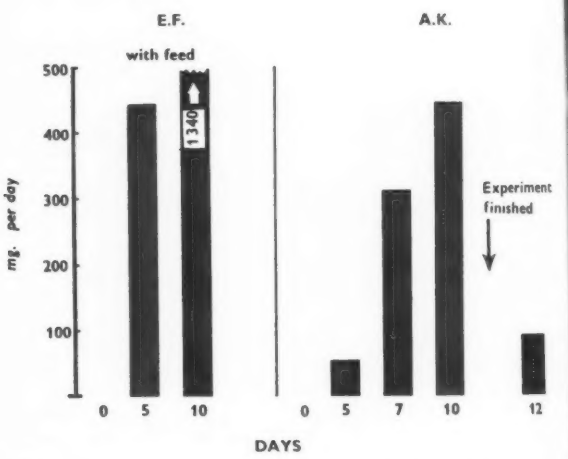

FIG. 10.—Daily proteinuria during feeding observations with galactose (E.F.) and milk (A.K.).

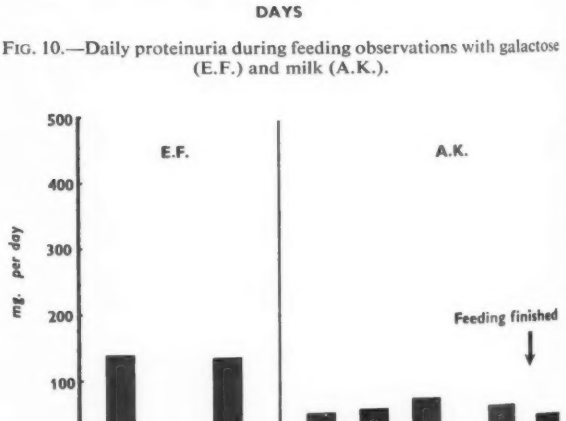

FIG. 11.—Daily excretion of urinary creatinine during feeding observations with galactose (E.F.) and milk (A.K.).

TABLE 7

PLASMA CO_2-COMBINING POWER ON MILK-FREE AND MILK DIETS

		Plasma CO_2 Combining Power (vol. per 100 ml.)	Urine *p*H
E.F.			
Galactose 20 g. daily × 10	June 27	26	
	June 28	29	6·2
Milk/galactose-free diet	Aug. 1	45	6·6
A.K.			
Milk/galactose-free diet	Mar. 10	62	6·42
Milk diet 8 days ..	Apr. 6	25	7·00
Milk/galactose-free diet	Apr. 27	50	5·63

The results, nevertheless, do give evidence (E.F., October 22, 1954) of an increase of serum chloride, diminished urine titratable acidity and ammonia content, with an increased urinary bicarbonate, suggesting that the acidosis may well be of renal origin (Table 8).

TABLE 8

SERUM AND URINE BIOCHEMICAL FINDINGS IN A GALACTOSE FEEDING OBSERVATION

		11.10.54 No Galactose	18.10.54 5 Days Galactose	22.10.54 10 Days Galactose
Serum	Cl. (mg. per 100 ml.)	608		632
	CO_2-combining power (vol. per 100 ml.) ..	54		50
Urine	NH_4 (mg. per 100 ml.). .	134	79	45
	Titratable acidity (Folin) (ml./100 ml.)	81	41	34
	$NaHCO_3$ (mg./100 ml.)	57	52	138
	Volume (ml.) per day ..	290	400	445

Blood and Plasma Phosphate Determinations

Quantitative estimations of inorganic and total acid-soluble phosphate in whole blood and in plasma were made on one occasion before and during galactose feeding.

The methods used were those of Kuttner and Cohen (1927) for the inorganic P and of Fiske and Subbarow (1925) for total acid-soluble P; the difference between these figures gave us the ester P figure. Thus it was possible to calculate the inorganic and ester P of the erythrocytes based on an assumed haematocrit of 45%. The selection of this figure for purposes of calculation was felt to be justified because, on the one hand, there was no evidence of haemoconcentration or any reason to suspect it and, on the other, any changes in the P content of the erythrocytes would be underestimated (Table 9).

The figures show a definite reduction in the amounts of inorganic and ester P in the erythrocytes after a régime of galactose feeding (Fig. 12).

The galactose-l-phosphate was estimated at the same time (Schwarz, Golberg, Komrower and Holzel, 1956) and showed a considerable increase (Table 9).

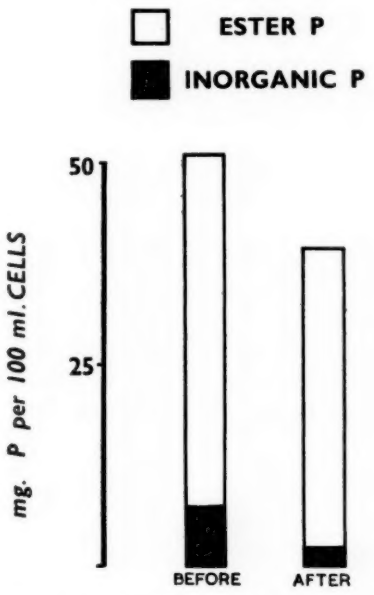

FIG. 12.—Inorganic and ester P in the erythrocytes before and after a period of milk diet (A.K.).

TABLE 9

BLOOD AND PLASMA P DETERMINATIONS IN A.K. (12 MONTHS) BEFORE AND AFTER ADMINISTRATION OF GALACTOSE

		Before Galactose (mg. per 100 ml.)	After Galactose (mg. per 100 ml.)
Blood	Inorganic P ..	6·62	4·14
	Total P	26·65	21·49
	Ester P	20·03	17·35
Plasma	Inorganic P ..	6·35	5·79
	Total P	6·55	7·25
	Ester P	0·20	1·46
	assuming a haematocrit of 45%, erythrocytes would contain		
R.B.C.	Inorganic P ..	6·96	2·13
	Ester P	44·27	36·78
Blood	Galactose-l-phosphate (free ester) ..	3·0	19·0

Studies of Erythrocyte Metabolism

A detailed description of the work carried out on certain aspects of erythrocyte metabolism in galactosaemia has been published (Schwarz *et al.*, 1956), and a summary of the findings will suffice here.

The oxygen uptake of normal erythrocytes is increased by the addition of galactose to a medium containing sub-optimal amounts of glucose. No such increase is observed with the erythrocytes of the galactosaemic patient.

The child's red cells after milk feeding have a lower oxygen uptake on a glucose substrate than the erythrocytes of the same individual before milk feeding is started (Fig. 13). Thus there is a partial inhibition of metabolism of red cells on the milk diet; furthermore, an accumulation of galactose-l-phosphate was found in these erythrocytes and this observation was paralleled

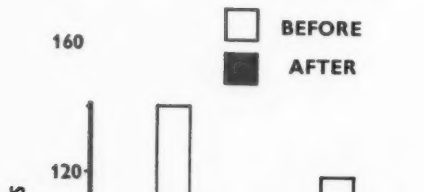

FIG. 13.—Respiration of the erythrocytes from galactosaemic patients before and after milk or galactose feeding.

in vitro when erythrocytes from galactosaemic patients were incubated in galactose-containing media (Fig. 14).

We have already stated that quantitative determination of inorganic and total acid-soluble phosphorus and, by difference, ester phosphorus in whole blood and plasma has revealed a fall in inorganic phosphate and total red cell phosphate esters and these changes lend support to the suggestion that normal metabolic processes are partially inhibited.

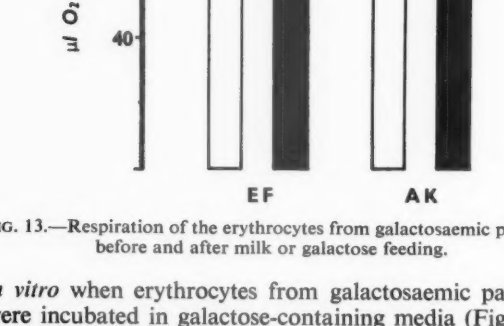

FIG. 14.—The accumulation of galactose-1-phosphate in normal and galactosaemic erythrocytes after incubation with galactose *in vitro*.

Discussion

It has frequently been suggested that galactose is a toxic substance (Cox and Pugh, 1954; Mitchell and Dodge, 1935; Bray *et al.*, 1952; Bruck and Rapoport, 1945; Donnell and Lann, 1951; Guha, 1931; Nelson, 1954) and that the clinical symptoms of galactosaemia are the result of galactose poisoning due to the accumulation of the sugar in the blood and tissues. It is difficult to verify this *in vivo* as it has been found impossible to produce blood levels of galactose comparable with those in galactosaemia by feeding the sugar to normal adults or near normal infants. From the work presented in this communication it seems possible that the classical symptoms of the disease may result from a disturbed cell metabolism due to the accumulation of galactose-1-phosphate in the tissues.

The presence of amino-aciduria, proteinuria and metabolic acidosis indicates a disturbance of the renal tubule which is, however, quickly corrected when milk or galactose is removed from the diet. The renal tubular upset does not extend to the excretion of potassium, sodium and water: the only careful observation we have been able to make of the salt and water excretion does not show any significant variation in the daily urinary excretion of these substances. One may postulate either a dysfunction of a particular portion of the renal tubule or a generalized disturbance of such a degree that only certain functions are affected.

It is also necessary to take into account the maturation of the kidney; the fact that, as the children grow older, it has proved easy to produce the proteinuria and amino-aciduria but not the acidosis, suggests a more rapid maturation of the tubule in respect of acid-base balance which is not paralleled in respect of protein and amino-acid re-absorption. In this context it is interesting to note that the average age of onset of idiopathic renal acidosis is approximately 6 months and that the disorder has corrected itself by the end of the second year of life (Latner and Burnard, 1950).

The figures for galactose excretion and retention indicate that an appreciable amount of hexose is utilized by the affected individual. This would suggest that the metabolic block is incomplete and hence it is likely that the severity of the defect will vary from one patient to the next. This is borne out in our clinical experience as there is considerable variation in the time of onset of symptoms and also in their severity. The two infants described here became ill during the first 10 days of life and, in our opinion, would have died had they not been treated promptly; there are other cases in our experience and in the literature where the symptoms did not

appear until 3 or 4 months of age or where the child presented in the second year of life with mental retardation, hepatomegaly and cataracts.

The question arises as to the mechanism by which the galactose is metabolized in these children. It is possible that the metabolism proceeds along the normal pathway although this channel is incapable of coping with the absorbed galactose quickly enough to prevent an elevation of the blood galactose level with consequent urinary excretion and accumulation in the tissues. Alternatively, a different metabolic pathway might be involved if the normal mechanism is completely inoperative, but this, too, is unable to deal with galactose at a satisfactory rate.

Hypoglycaemia has been reported by several investigators to follow the administration of milk or galactose to a galactosaemic patient (Bruck and Rapoport, 1945; Cusworth *et al.*, 1955; Hudson *et al.*, 1954; Mason and Turner, 1935; Norman and Fashena, 1943). We have shown that the blood glucose may fall precipitously during a galactose tolerance test, but that on an ordinary milk diet the degree of hypoglycaemia is slight. It is very unlikely that any of the symptoms of galactosaemia could result directly from this mild hypoglycaemia, when similar symptoms are not apparent in conditions of more severe hypoglycaemia. On the other hand, the relative deficiency of glucose might well aggravate a condition arising from the partial inhibition of glucose metabolism. The aetiology of the hypoglycaemia associated with galactosaemia is still obscure, but in accordance with our hypothesis the galactose-l-phosphate, which would be expected to accumulate in the liver more rapidly than elsewhere, might well inhibit glycogenolysis and thus lead to a lowering of the blood sugar.

On account of the possibly disastrous fall in blood glucose during a galactose tolerance test, the diagnosis of galactosaemia should be made by other means whenever this can be done and the galactose tolerance test only used when the diagnosis is still in doubt.

We have not found any galactose in the blood of treated cases (c.f. Hartmann, Grunwaldt and James, 1953), and believe that the absence of the sugar is attributable to the careful exclusion of all lactose from the diet in our cases.

It has been shown elsewhere that the metabolic defect of galactosaemia is present in erythrocytes (Schwarz *et al.*, 1955). Recently Kalckar, Anderson and Isselbacher (1956) have determined the uridyl transferase content of the erythrocytes from normal and galactosaemic infants, and have established that the enzyme is absent from the red cells of the latter. It is very likely, therefore, that it is the deficiency of this enzyme which is responsible for the faulty metabolism of galactose in the liver. The presence of the specific defect in erythrocytes suggests that many other tissues may be similarly affected. Since exposure of galactosaemic erythrocytes to galactose, *in vivo* or *in vitro*, results in the accumulation of galactose-l-phosphate and in a partial inhibition of the normal glucose metabolism of these cells, a similar process may be imagined to take place in other tissues. In this way a curtailment of energy-yielding reactions may account for the observed dysfunction of kidney, liver, brain and lens tissues.

The evidence obtained from experiments *in vitro* with erythrocytes suggests that galactose itself has no toxic action on normal cells. It may well be that the accumulation of galactose-l-phosphate, which is peculiar to galactosaemic cells, is responsible for the partial inhibition of glucose metabolism. Thus the actual toxic agent may prove to be galactose-l-phosphate, or a metabolite derived from it. This would explain why some of the signs of galactosaemia, e.g., the amino-aciduria, persist for several days after the cessation of galactose feeding, although the blood galactose level has already returned to zero. Similarly, the amino-aciduria does not appear until four or five days after the beginning of galactose feeding, although blood levels are built up rapidly and galactose is excreted in the urine from the first day.

According to this concept it is the relative amounts of galactokinase and of the uridyl transferase and galactowaldenase system in a particular tissue which determine the rate of accumulation and disappearance of galactose-l-phosphate, and since there may be local variations in the ratio of these enzymes, one would expect a greater accumulation in a tissue where the ratio is high and hence a disturbance of function of that particular tissue.

The hypothesis presented appears to give a reasonable explanation of the widespread and frequently reversible symptoms and signs of galactosaemia which are described in our two cases and in those previously reported by other authors.

Summary

Two further cases of galactosaemia are presented with the results of clinical and biochemical investigations.

The effect of milk or galactose feeding for eight- or 10-day periods is described, with particular reference to blood glucose and galactose levels, galactose excretion, renal function and blood and plasma phosphorus levels.

Reference is made to the work carried out in

certain aspects of erythrocyte metabolism in this disease.

The causation of the signs and symptoms of the disease is discussed in the light of the findings reported in this communication. The hypothesis is put forward that the varied manifestations of galactosaemia may be attributed to localized accumulation of galactose-l-phosphate within the tissues, and that the extent to which such accumulation occurs—and consequently the resulting lesion or impairment of function—is determined by the ratio of local concentration of enzymes concerned with the early stage of galactose metabolism.

We are particularly indebted to Mr. H. Varley (Manchester Royal Infirmary) and Miss V. K. Wilson (Royal Manchester Children's Hospital) for carrying out certain biochemical investigations, to Dr. S. W. Stanbury for his help and valuable criticism and to the Department of Medical Illustration for photographs and reproductions; also to Dr. Margaret Egan who so kindly sent to us the second case. We wish to thank Miss Anne Walton, recently sister-in-charge Infants' Ward, St. Mary's Hospitals, Manchester, who was in charge of these children throughout the investigations. Finally, we wish to record our appreciation of the support we received from Professor A. C. P. Campbell and Professor W. F. Gaisford.

One of us (V.S.) was assisted by a grant from Cow and Gate Limited, Guildford, Surrey.

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APPENDIX

The following are details of the feeding régimes during the periods of observation.

E.F.

I Jan. 1953 (aged 18 months). Wt. 19 lb. 1 oz. 20 g. of galactose added daily to lactose-free toddlers' diet.

II 11.10.54 (aged 3 years 4 months). Wt. 23 lb. 24 g. of galactose daily given in divided doses for 10 days.

A.K.

III 30.3.54 (aged 14 weeks). Wt. 9 lb. 14 oz. Half-cream National dried milk: 5½ oz.×5 daily, for 8 days (1 drachm (3·9 g.) glucose added to each 5½ oz. feed).

IV 21.6.54 (aged 6 months). Wt. 12 lb. 5 oz. Galactose 15 g. daily added in divided doses to the special feed for six days. The special feed contained egg, 'farex' and dextrimaltose and had a high carbohydrate content.

V 20.11.54 (aged 11 months). Wt. 17 lb. 8 oz. Galactose 20 g. daily for four days, increased to 24 g. daily for a further six days, while child was on a weaning diet plus special feed described above.

On all occasions a detailed statement was made about the food intake and rejection; all the galactose was given and any vomited was replaced.

ADDISON'S DISEASE IN INFANCY

BY

ALAN WILLIAMS and M. J. ROBINSON
From the Royal Children's Hospital, Melbourne

(RECEIVED FOR PUBLICATION MARCH 20, 1956)

Addison's disease may occur in infants with the adrenogenital syndrome, the adrenals being structurally intact and larger than normal. However, Addison's disease comparable with that occurring in adults also occurs in infants whose adrenal glands are hypoplastic or diseased. These infants fail to gain weight and are in a poor state of hydration despite a theoretically adequate caloric and fluid intake. They also have weakness, diarrhoea, vomiting and skin pigmentation as features of their illness. Death may be sudden following circulatory failure in a typical 'Addisonian crisis' if the condition is not recognized and treatment instituted. We have been able to find in the English literature records of only nine infants with Addison's disease due to adrenal hypoplasia or adrenal destruction.

This paper summarizes the literature, and records four additional cases. Three of these infants died suddenly, the terminal illness in each case suggesting acute adrenal insufficiency. The fourth is at present under treatment and progressing satisfactorily.

Case Reports

Case 1. A.S., a boy, was aged 10 weeks and weighed 7 lb. 5 oz. when admitted to the Royal Children's Hospital, Melbourne. Pregnancy and labour had been uneventful, and his birth weight was 7 lb. 7½ oz. His mother thought the baby was thriving until she took him to a health centre when he was 4 weeks of age and found his weight to be 7 lb. 5 oz. He was taking 4-5 oz. of breast milk seven or eight times daily. Seven weeks later because his weight was unchanged he was referred to hospital. A week before admission he had diarrhoea with three or four green watery stools daily. When examined he was mildly dehydrated, the tissue turgor being diminished and his tongue dry. Pigmentation of the scrotal, perianal and areolar skin was noticed but its significance was not initially appreciated as the baby's parents were dark-skinned Italians. The blood pressure was 80/60 mm. Hg. No definite diagnosis was made, and the babe was observed.

For the first eight days he took feeds well but although his intake was greater than his estimated requirements he did not gain weight. On the eighth day he developed slight diarrhoea, became lethargic and required gavage feedings. The next day he was found moribund with circulatory failure and gross dehydration. Twitching developed and he was given phenobarbitone with little response. Clinical signs suggested that he had developed acute bronchopneumonia and he was given intravenous saline and tetracycline. Over the next 24 hours his condition improved and intravenous therapy was suspended. However, he fed poorly and two days later, in the absence of vomiting and diarrhoea, became grossly dehydrated, again requiring intravenous fluid.

The possibility of Addison's disease was suggested by the following serum electrolyte levels.

Serum	sodium	120 mEq. per l.
,,	potassium	9 mEq. per l.
,,	calcium	4·6 mEq. per l.
,,	chloride	96·0 mEq. per l.
,,	bicarbonate	29 mEq. per l.
,,	phosphate	3 mEq. per l.

Other investigations gave: Haemoglobin 7·9 g. per 100 ml., W.B.C. 5,850 per c.mm. (differential cell count normal); serum proteins 6·2 g. per 100 ml. (albumin 2·56, globulin 3·64); blood urea 30 mg. per 100 ml.; fasting blood sugar (three estimations) 16, 17, 64 mg. per 100 ml.

Analysis of urine revealed a 24-hour output of 17-hydroxysteroids = 0·045 mg., and of 17-ketosteroids = 0·7 mg. The serum 17-hydroxysteroid level was less than 2 micrograms per 100 ml. (normal = 5-6 micrograms per 100 ml.). These specimens were taken one week after the baby had been given 10 mg. A.C.T.H. on alternate days.

During this period of investigation there had been no weight gain; the baby had taken feeds slowly and although obtaining theoretically adequate fluid had remained slightly dehydrated throughout.

Treatment was begun with 25 mg. cortisone by mouth twice daily. His general condition and weight remained unchanged and 10 days later he was again dehydrated.

At this stage 4 g. sodium chloride was added to the total daily feedings and the result was dramatic (Fig. 1). In the following five days he gained 1 lb. 5 oz., he was in perfect hydration and taking almost double the quantity of feeds. There was no sign of oedema, glycosuria or elevation of blood pressure and the baby was more active and a much better colour. During the next two weeks he had gained another 1 lb.

The serum electrolytes were now normal, the blood

sugar level was 100 mg./100 ml., and he was discharged from hospital.

When last seen at the age of 7 months his weight was 15 lb. He appeared normal in all respects and the pigmentation was much less noticeable. He is at present receiving 12·5 mg. cortisone daily and 3 g. sodium chloride added to his total daily feeds.

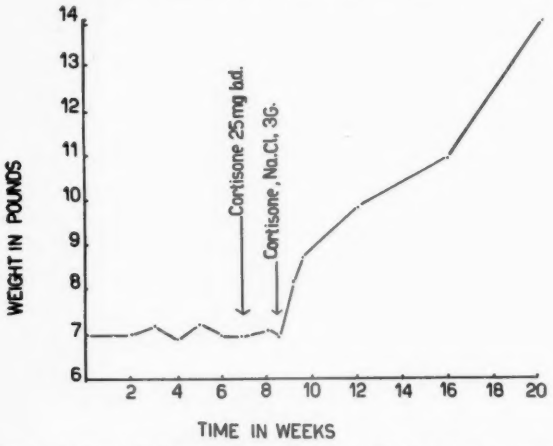

FIG. 1.—Case 1: Chart showing gain of weight following treatment with cortisone and sodium chloride.

Case 2. K.C., a 13-month-old girl, was admitted to the Royal Children's Hospital, Melbourne, in December, 1948, in a moribund condition. Heat wave conditions were prevailing at the time. She had been born at term after an uncomplicated labour, the birth weight being 8 lb. 13 oz. She had thrived since birth until her present illness which began 36 hours before admission with vomiting and refusal to take feeds. These symptoms persisted and were accompanied by intermittent crying until admission.

When examined the baby was pale and comatose. Generalized twitching was noted and the temperature was 108° F. A definite diagnosis was not possible and the baby died one hour after admission.

At necropsy the only abnormalities noted were that the lungs were congested and slightly oedematous, and both adrenals were small and contained areas of calcification. Microscopically, little cortical and no medullary tissue was present. A large area of amorphous material was surrounded by a fibrous capsule in which groups of cortical cells were present (Fig. 2). Abundant haemosiderin pigment and calcium could be seen in this fibrous tissue.

In summary, this infant had progressed normally despite extensive destruction of both adrenals until the age of 13 months. The combination of a respiratory tract infection and extremely hot weather caused death in an Addisonian crisis.

Case 3. R.G., a boy, was admitted to this hospital at the age of 4 weeks in July, 1948. He was said to have been two weeks postmature at birth and was noted to be very feeble. At the age of 2 weeks the baby began

FIG. 2.—Case 2: A small amount of adrenal cortex is shown in thick fibrous tissue capsule. Haemosiderin and calcium are present in fibrous tissue and in underlying amorphous material. (Haemotoxylin and eosin ×90.)

to vomit and became dehydrated. The vomiting persisted and at times appeared projectile. For this reason he was admitted to hospital for investigation. The birth weight was 6 lb. 7 oz. and the weight on admission 5 lb. 12 oz. A fine papular rash covered most of the body but apart from this no abnormality was noted. Vomiting persisted and feeds were taken very slowly, and an intragastric drip was required. Ten days after admission, the baby suddenly became grossly dehydrated. This occurred in the absence of vomiting and diarrhoea. The hydration was restored with intravenous therapy, but could not be maintained and death was sudden 18 days after admission.

While the baby was in hospital the following investigations were performed and results found to be normal: Chemical and microscopic examination of urine and cerebrospinal fluid; radiographic examination of heart and lungs; a barium meal and a peripheral blood examination.

Post-mortem examination revealed minimal bronchopneumonia. The only other abnormality detected on macroscopic or microscopic examination was the presence of extremely small adrenal glands (approximately one-sixth the volume for normal glands at this age. On histological examination the adrenal cortex appeared well differentiated and was separated from well

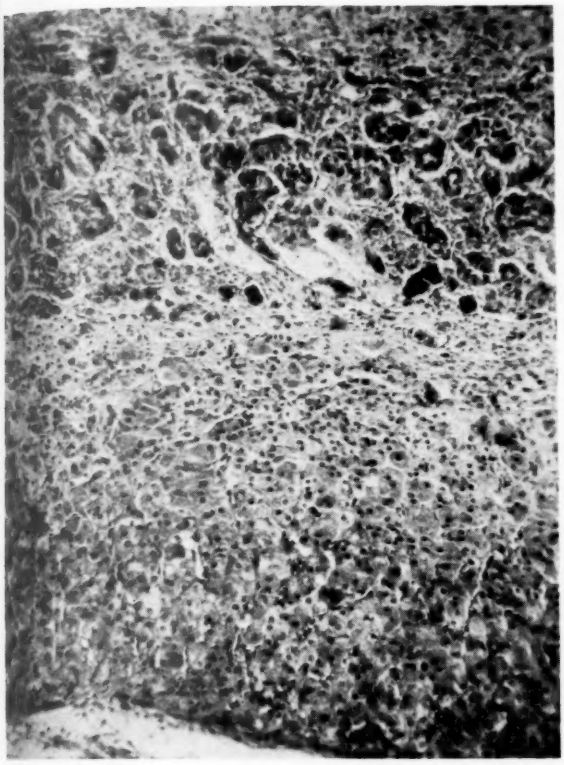

FIG. 3.—Case 3: Calcium and haemosiderin granules in fibrous tissue adjacent to well formed medulla. (Haemotoxylin and eosin ×105.)

formed medullary tissue by a thin layer of fibrous tissue. In this tissue deposits of calcium and haemosiderin were present (Fig. 3).

It would appear that in this child the symptomatology of adrenal insufficiency began shortly after birth and that death occurred in an Addisonian crisis.

Case 4. K.F., a girl, was aged 2 days when admitted to this hospital in July, 1951. Birth was normal, but some hours later vomiting began. The only abnormalities noted on examination were a mild degree of jaundice and a palpable spleen. The provisional diagnosis of erythroblastosis foetalis was not confirmed by serological investigation. The jaundice completely subsided in about one week, but the baby remained lethargic, vomited persistently and refused feeds. Investigations included chemical and microscopic examination of urine, radiography of the skull and chest; blood urea and a barium meal were normal. Two weeks after admission the baby had become dehydrated, the skin was noted to be a dirty grey colour and intravenous therapy was begun. The baby developed acute bronchopneumonia and died 24 hours later.

At necropsy extensive bronchopneumonia was present. Both adrenals were hypoplastic, approximately one-quarter of their normal size. Microscopic examination revealed a well formed definitive cortex, immediately adjacent to medullary tissue. The zone of connective tissue representing condensation of stroma of the foetal zone which is usually seen at this age was absent. There was no evidence of calcification or haemorrhage.

This history is compatible with adrenal insufficiency, death being precipitated by acute bronchopneumonia.

Discussion

From the clinical notes of our own and the recorded cases (Table 1) a definite syndrome emerges. The features are failure to gain weight, dehydration despite a theoretically adequate fluid intake and skin pigmentation. These infants are sluggish, feed poorly and are subject to episodes of vomiting and diarrhoea. Addison's disease should be considered in any infant whose illness manifests this combination of features. Diagnosis and institution of treatment should be made without delay as sudden circulatory collapse followed by death may occur. In two of our cases and seven of the nine recorded cases death occurred suddenly in an Addisonian crisis.

Diagnosis of Addison's disease in an infant is suggested by the demonstration of a typical electrolyte pattern in the serum and confirmed by a low 17-hydroxysteroid level in the urine. The levels of sodium, chloride and bicarbonate in the serum are low and that of potassium elevated. These deviations from normal are more pronounced in a crisis. A similar serum electrolyte pattern is occasionally seen in some forms of renal disease, which should be excluded by examination of urine and blood urea estimation.

Clinical features and laboratory findings identical with the above may be seen in infants with adrenal hyperplasia resulting in female pseudo-hermaphroditism and macrogenitosoma praecox. The former is readily recognized by the characteristic genital anomaly, but in the diagnosis of the latter estimations of urinary 17-ketosteroids may be needed. These are elevated (above 1 mg. per 24-hour specimen) in adrenal hyperplasia but are low in adrenal hypoplasia. Final proof of the correct diagnosis is shown by the disappearance of signs and symptoms with substitution therapy.

In the treatment of a crisis adequate fluid, sodium, chloride and glucose must be rapidly supplied. The most satisfactory method is via the intravenous route, amounts required depending on the state of hydration and electrolyte depletion. Cortisone alone, or in combination with D.O.C.A., is also required. Although most authorities have recommended maintenance with D.O.C.A., it is our impression that cortisone with its hyperglycaemic action is more effective. From analysis of the reported cases and from personal observations, hypoglycaemia is a feature of this illness in infants.

TABLE 1
SUMMARY OF RECORDED CASES OF ADDISON'S DISEASE IN INFANCY

Author	Age	Clinical Features	Investigations	Treatment	Mode of Death	Necropsy Findings
Jaudon (1946a)	4½ months	Anorexia, diarrhoea, listlessness, vomiting, loss of weight, pigmentation	Serum electrolytes supported diagnosis of Addison's disease. Low blood sugar. Positive Mantoux test	D.O.C.A. plus sodium chloride	—	—
Sikl (1948)	33 days	Failure to thrive, diarrhoea, pigmentation	—	—	Sudden death soon after admission	Hypoplasia of adrenals
Roberts (1949)	3 weeks	Vomiting, failure to thrive, dehydration	Serum electrolytes supported diagnosis of Addison's disease	Adrenal cortical extract and sodium chloride	Well until 6 months. Died suddenly	Hypoplasia of adrenals
Deamer and Silver (1950) ..	*Case 1* 2½ months	Vomiting, failure to gain weight, pigmentation	Serum electrolytes supported diagnosis of Addison's disease	D.O.C.A. and sodium chloride, pellets later implanted	Sudden death aged 6 months after fever, convulsions, diarrhoea and vomiting	Hypoplasia of adrenals
	Case 2 19 months	Anorexia, vomiting, weakness, craving for salt	Electrolytes supported diagnosis of Addison's disease	D.O.C.A. and sodium chloride	—	—
Moore and Cermak (1950)	3 weeks	Vomiting, diarrhoea, pigmentation	Serum electrolytes supported diagnosis of Addison's disease	D.O.C.A. and sodium chloride	Sudden death	Bilateral adrenal cysts
Geppert *et al.* (1950)	8 months	Vomiting, failure to gain weight, pigmentation	Serum electrolytes supported diagnosis of Addison's disease	D.O.C.A. and sodium chloride	Sudden death following convulsions	Hypoplasia of adrenals
Provenzano (1950)	11 days	Failure to gain weight, dehydration	—	Adrenal cortical extract and sodium chloride	Sudden death aged 21 days after convulsions	Hypoplasia of adrenals
Welsh and Mehlin (1954) ..	18 hours	Collapse and pigmentation	—	—	Sudden death at 24 hours	Hypoplasia of adrenals

Several of the recorded infants died following convulsions (Table 1). It would appear feasible that the convulsions were related to profound hypoglycaemia as low blood sugar levels were recorded in several cases. Random blood sugar estimations in our Case 1 gave low results, the level on three separate occasions being 17 mg., 18 mg. and 64 mg./100 ml. Cortisone rather than D.O.C.A. is likely to control this abnormality. In addition, cortisone has slight salt-retaining properties, and if used with additional salt in the diet allows good electrolyte control and obviates daily injections or implantation of pellets. That this therapy has been completely successful in our case is shown by the complete resolution of clinical signs and symptoms and the good biochemical control achieved. Neither long-term prognosis nor duration of treatment can be discussed from the available data as the duration of follow-up periods has been relatively short. The prognosis and duration of treatment will depend on two factors: (1) whether the adrenal lesion is progressive and (2) whether the adrenal cortex can regenerate.

The adrenal abnormality most commonly recorded in these infants has been cortical hypoplasia. This condition, which is usually associated with anencephaly, was found at necropsy in six of the recorded cases (Table 1) and in two of the three infants in our series. In Cases 3 and 4 the adrenals resembled those seen in anencephalic monsters, i.e., well formed definitive cortex, little evidence of foetal cortex and an increased amount of medullary tissue. In Case 3, in addition, haemosiderin and calcium were present in the fibrous tissue separating cortex from medulla. This appearance suggests that haemorrhage and replacement fibrosis had been at least partly responsible for the grossly diminished size of the adrenals in this infant. In view of the association with anencephaly the central nervous system and pituitary glands were studied but no abnormality was detected.

Destruction of adrenal tissue in Case 2 appears

to have been caused by haemorrhage, abundant haemosiderin pigment as well as fibrous tissue and calcium being present in sections. It is difficult to estimate when the adrenal haemorrhage occurred. The relative frequency with which adrenal haemorrhage occurs at birth and the knowledge that such haemorrhage is not always immediately fatal (Potter, 1952; Snelling and Erb, 1935; Emery and Zachary, 1952) suggest that it occurred at this time. Adrenal insufficiency became clinically manifest 13 months later when the presence of a respiratory tract infection and a bout of extremely hot weather coincided. During this same period of hot weather another infant aged 3 months died suddenly in this hospital. This infant was spastic, presumably following cerebral damage during birth which had been a difficult forceps delivery. He had been in hospital since birth and during that period his weight had remained stationary. He died unexpectedly 24 hours after the onset of severe dehydration accompanied by a sudden temperature rise to 107° F. Necropsy disclosed bronchopneumonia which was not extensive, and adrenals in both of which haemorrhage had occurred as judged by the presence of haemosiderin, fibrosis and calcification. There was little normal cortical tissue, the histological appearances of the adrenals resembling those of Case 2. (This infant is not included in the case reports as cerebral palsy dominated the clinical picture.)

Similarly the adrenals of Cases 3 and 4 had almost certainly been considerably diminished in size since birth and it is difficult to account for the lack of any evidence of regeneration in these adrenals with non-progressive lesions in view of the knowledge that adrenal cortex regenerates readily in experimental animals. This lack of regeneration was not only present in the hypoplastic adrenals where a functional pituitary abnormality may have been the primary cause, but also in those where haemorrhage had caused destruction of tissue.

There is evidence to suggest that temporary adrenal insufficiency may occur. Jaudon (1946b, 1948) records a series of 14 infants whose clinical and laboratory findings satisfy the diagnostic criteria of Addison's disease. They responded to substitution therapy with recurrence of clinical features upon its cessation. After periods varying from five to 29 months it was possible to stop treatment without recurrence of symptoms.

Summary

Addison's disease occurs in infancy and may be due to hypoplasia or destruction of the adrenal glands. The features of the illness are failure to gain weight, dehydration, vomiting and pigmentation. Death may occur suddenly in an Addisonian crisis.

Diagnosis is supported by detection of a typical pattern of serum electrolytes with low sodium, chloride and bicarbonate levels and elevated potassium. There is also a lowered urinary excretion of 17-hydroxysteroids.

The clinical notes are presented of an infant in whom the signs and symptoms of Addison's disease rapidly responded to treatment with cortisone and sodium chloride.

The histories of three infants in whom adrenal hypoplasia or destruction of adrenal tissue by haemorrhage was found at post-mortem examination are recorded. These lesions of the adrenals were considered responsible for features of Addison's disease during life.

A brief summary of nine similar recorded cases is tabulated.

We wish to thank Dr. S. W. Williams, under whose care A.S. (Case 1) was admitted, for permission to publish this case.

We also thank Dr. B. Hudson, and Dr. J. Bornstein for estimating the serum and urinary ketosteroids and hydroxysteroids in Case 1.

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FIBROCYSTIC DISEASE OF THE PANCREAS IN AN ADOLESCENT WITH MINIMAL PULMONARY INVOLVEMENT

BY

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(RECEIVED FOR PUBLICATION MARCH 20, 1956)

Fibrocystic disease of the pancreas is a congenital condition seen most frequently in infancy and early childhood, resulting from the production of excessively viscid mucus in the alimentary and respiratory tracts. It may present within the first few days of life as acute intestinal obstruction, resulting from meconium ileus, and is characterized clinically in later infancy and childhood by steatorrhoea, retarded growth, progressive bronchiectasis and pulmonary fibrosis and, on occasions, cirrhosis of the liver. Two unusual but probably related features make the present case worth recording, namely, the healthy survival of the patient to his present age (16 years) together with the minimal involvement of the respiratory system.

Case Report

R.B. was born at full term of a mildly toxaemic mother on February 3, 1940. He weighed 9½ lb. From birth his bowels were opened up to 10 times daily with the passage of bulky, offensive, greasy stools and for the first four months his weight fluctuated between 7¼ and 9½ lb. Thereafter it slowly increased. At 1 year he had measles complicated by rectal prolapse, and at the age of 2 he was admitted to the Middlesex Hospital for investigation of steatorrhoea. Stool analysis at that time revealed 49·4% fat content, of which 45·1% was unsplit, while microscopy showed numbers of undigested meat fibres with many starch granules. Treatment with a low-fat diet was instituted but the bowel symptoms remained unaltered. Apart from two episodes of pneumonia and a recurrent winter cough, he remained well, although under weight, until his admission to St. Bartholomew's Hospital on July 12, 1954, with a 24-hour history of intermittent severe colicky lower abdominal pain. He had vomited on four occasions but his bowels had been opened only twice, the stools being of much smaller volume than normal and containing no blood. There was no relevant family history; his mother and younger sister were well, although his father suffered from epilepsy.

On examination he was under weight for his age : height 5 ft., weight 5 stone 9¼ lb. There were no secondary sex characteristics and the testes and penis were small. He was flushed and anxious with a temperature of 99·4° F., pulse rate 130, respirations 24. The tongue was furred, the heart and lungs appeared healthy but there was well marked clubbing. The abdomen was not distended. Peristaltic waves were visible to the left of the umbilicus, and in the right iliac fossa there was a mobile, sausage-shaped mass which was acutely tender on pressure. Rectal examination was normal. A diagnosis of intussusception was made, and the symptoms and signs resolved within 12 hours. Investigations were then begun to elucidate the nature of the steatorrhoea, with the following results:

Haemoglobin 96% (Haldane); white blood count 7,000 per c.mm. (differential count normal); E.S.R. 6 mm. in one hour (Westergren); urine, no albumin or sugar; serum calcium 10·5 mg. per 100 ml.; serum inorganic phosphate, 3·8 mg. per 100 ml.; plasma proteins, albumin 4·6 g. per 100 ml. and globulin 1·8 g. per 100 ml.

The serum antithrombin level was normal (MacFarlane's technique).

A glucose tolerance test gave a fasting blood sugar of 88 mg. %, and after 50 g. dextrose, 94 mg. (½ hour), 103 mg. % (one hour), 88 mg. % (1½ hours), 69 mg. % (two hours).

Stool microscopy showed large numbers of undigested and partially digested muscle fibres. A fat balance over four days gave 68% absorption.

Duodenal intubation showed on two occasions yellow viscous alkaline juice, but no tryptic activity could be detected by the Horsfield method.

The sputum was yellowish green and mucopurulent. Culture yielded a mixed growth of *Staph. pyogenes* and *Haemophilus influenzae*.

The Mantoux test was negative to 1 in 100.

A radiograph of the chest (Fig. 1) in both upper zones showed streaky linear shadowing, and on the more penetrated film there was a honeycomb appearance in the left cardiophrenic region.

On a bronchogram (Fig. 2) the bronchi on both sides appeared normal.

Both antra were opaque radiologically.

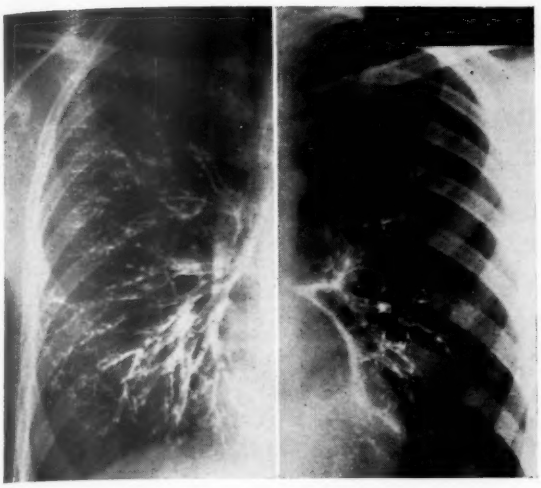

FIG. 2.—The normal bronchogram.

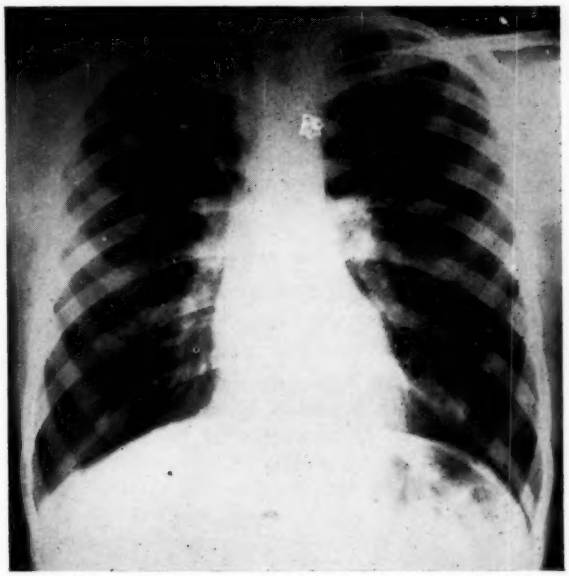

FIG. 1.—Chest radiograph showing linear upper zone shadowing and honeycomb appearance in left cardiophrenic region.

On a barium follow-through the jejunum appeared normal, but the ileum was dilated and contained excess gas. There was poor coating of the mucosa by the barium consistent with the presence of excess fat. Similar changes were seen in the colon, which was rather dilated.

A diagnosis of fibrocystic disease of the pancreas with minimal pulmonary involvement was made. Treatment was begun with a triple strength pancreatin compound ('panteric 503', Parke Davis) grains 10 three times a day with meals. There was an immediate improvement in the frequency and character of the stools, the bowels being opened only two to three times a day and the stools being much less bulky and offensive. Over the next 12 months he gained 4 in. in height and 17 lb. in weight, but the productive cough has continued unchanged. He is now aged 16 and is working as a full-time photographer's assistant.

Discussion

The diagnosis of fibrocystic disease was suggested by the history of steatorrhoea from birth associated with a chronic cough, while confirmation was obtained by the analysis of duodenal juice aspirated on two separate occasions. The development of intussusception has been noted before in fibrocystic disease (Norman, 1954a) and its occurrence was probably coincidental. The normal antithrombin titre is unusual but Norman (1954b) has pointed out that only 90% of children with proven fibrocystic disease show a significantly reduced level. The appearances seen on the plain radiograph of the chest, in particular the streaky linear upper zone shadowing, are suggestive of quiescent pulmonary tuberculosis. This diagnosis is, however, hardly compatible with a negative Mantoux test to a dilution of 1/100. It seems reasonable, therefore, to ascribe the changes to a degree of peribronchial fibrosis resulting from a chronic low-grade bronchial infection.

Although the condition has, in the past, been considered to be a disease of infancy and childhood, there are now many isolated reports of protracted survival. Parmelee (1935) collected a group of cases of which the oldest was 14 years, while Pugsley and Spence (1949) reported the survival of a patient to the age of 17. Hendrix and Good (1956) gave a detailed account of a patient who survived to the same age, while a clinico-pathological conference (1954) on fibrocystic disease of the pancreas held at the Hammersmith Hospital was concerned with a man who died at the age of 19 years and 9 months. Even more striking was the patient described by Burnard (1953) who was able to continue his normal occupation at the age of 23 despite severe respiratory involvement and persistent abdominal symptoms. With one exception all these patients were dead and post-mortem examination had revealed the presence of gross bronchiectatic changes. Burnard's case was still alive at the age of 23, but a bronchogram had demonstrated the presence of diffuse cylindrical bronchiectasis two years previously. Emphasis has very rightly been laid on the importance of antibiotics in the continued survival of such patients. In the case recorded here, however, antibiotics have not been used because, although the pulmonary condition is severe enough to cause a chronic productive cough

and minimal radiological changes, it has not advanced sufficiently to produce either severe systemic symptoms or any definite bronchographic evidence of bronchiectasis. The absence of severe pulmonary involvement in a patient of this age with proven fibrocystic disease is a most unusual finding, and is undoubtedly the explanation of his continued healthy survival.

Summary

The account is given of a patient with fibrocystic disease of the pancreas whose admission to hospital was precipitated by an episode of intussusception.

Although now aged 16, the patient is living a normal healthy life with minimal respiratory or alimentary symptoms.

An unusual feature of this case is the absence of gross pulmonary changes, and it is to this that the patient's continued good health is probably due.

I am grateful to Dr. K. O. Black for permission to publish this case and to Dr. A. W. Franklin and Dr. A. P. Norman for their opinions. My thanks are also due to Dr. R. Kemp Harper for his interpretation of the radiographs and to Dr. W. G. Dangerfield for the analyses of duodenal juice.

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ACUTE PANCREATITIS IN CHILDHOOD

BY

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(RECEIVED FOR PUBLICATION APRIL 16, 1956)

Acute haemorrhagic pancreatitis in childhood is an uncommon disease, so that, although the signs and symptoms are as typical as in the adult when it does occur, it is usually undiagnosed pre-operatively as the possibility has not been included in the differential diagnosis.

When Dobbs (1935) reported a case he found only 14 previous cases in the world literature. Ger (1954) and Boss (1955) have each described one further case.

It is intended therefore to record two further cases and summarize the available information regarding diagnosis, aetiology and treatment.

Case Reports

Case 1. L.C., a girl aged 4 years, was admitted in September, 1954. She had a history of possibly having swallowed a stone while playing in the garden. One hour later she complained of sudden severe epigastric pain and vomiting, in consequence of which she was brought up to the Casualty Department. She appeared pale and slightly shocked and had tenderness and guarding localized to the epigastrium. An upright radiograph did not reveal a radio-opaque foreign body or any air under the diaphragm. She was admitted for observation. Her temperature was 97·8° and pulse 136.

She continued to vomit at frequent intervals and became more shocked with a rising pulse rate. Generalized rigidity with abdominal distension and absent bowel sounds rapidly developed. The urine contained sugar and acetone and the blood sugar estimation was found to be 232 mg. %. The leucocyte count was 20,000 per c.mm. A diagnosis of peritonitis of uncertain origin was made and an immediate laparotomy was decided upon. Gastric suction and intravenous therapy were instituted.

OPERATION. A right mid-paramedian incision was made under general anaesthesia. The peritoneal cavity contained a considerable quantity of opalescent, mildly blood-stained fluid. The whole bowel showed the gross injection associated with peritonitis. All the lacteals in the mesentery were sharply outlined white by engorgement with chyle. The omentum and mesentery showed numerous raised, cream-coloured nodules with an injected surround. These could not be wiped off and were considered to be fat necrosis. Part of the greater omentum containing such plaques was excised for histology.

No lesion of the alimentary tract itself was found and the gall bladder appeared normal but would not empty on compression. A large oedematous mass was palpated behind the stomach in the situation of the head and body of the pancreas. The oedema also spread forwards into the transverse mesocolon.

A diagnosis of acute haemorrhagic pancreatitis was made and the abdomen closed without further interference or drainage.

PROGRESS. Post-operatively penicillin and streptomycin were given intramuscularly and gastric aspiration and intravenous fluids continued.

It was found that the urinary diastase (estimated by King's method) on urine which had been collected pre-operatively was 160 units per ml. and the serum amylase was 9,600 units %.

For two days her general condition was poor but on the third day bowel sounds returned and her general condition improved. The serum amylase (estimated by King's method) fell to 533 units %. Thereafter she made an uninterrupted recovery. Urine specimens since that time have not contained sugar or acetone and the blood sugar levels have remained normal.

HISTOLOGICAL REPORT. The specimen consisted of a piece of omentum on which were numerous small white plaques. Sections showed many small areas of early fat necrosis. In most areas complete small lobules were degenerate and there was then no cellular reaction. The peritoneum showed some proliferation and scanty infiltration by polymorphs and mononuclear macrophages.

Case 2. E.R., a boy aged 4½ years, was admitted in November, 1955, with a history of persistent vomiting and right-sided abdominal pain for 48 hours, having been off colour with a poor appetite for three weeks and constipated for four days.

The temperature was 100·8° F. and pulse 140. He was ketosed and markedly dehydrated. The abdomen was scaphoid and guarding was maximal in the epigastrium and right upper quadrant but no rebound tenderness was elicited. No mass could be felt and bowel sounds were absent. The white blood count was 23,000 per c.mm. Intravenous and antibiotic therapy was started and laparotomy undertaken. There was considerable free fluid in the peritoneal cavity. Patches of fat necrosis were observed, particularly on the

omentum and a mass 2 by 3 in. was felt in the region of the head of the pancreas. The abdomen was closed without definitive surgery.

Post-operatively probanthine, 15 mg., was given six-hourly and gastric aspiration and intravenous therapy continued. On the day following operation the urinary diastase was 160 units per ml. His improvement was slow over the next week. By the tenth day the serum amylase was still 640 units % and the urinary diastase 60 units per ml. During the subsequent two months the serum amylase fluctuated between 266 and 457 units %.

A barium meal and cholecystogram showed no abnormality and the blood sugar curve was normal. Fat absorption was poor as shown by no detectable iodine in the 12-18 hour specimen after an oral dose of 8 ml. of 'lipiodol'.

These two patients represent the two forms of iodiopathic pancreatitis in children, the former the acute type with dramatic onset and rapid resolution, and the latter the more subacute onset with a more protracted course.

Below is a summary of recorded cases with the outcome and suggested aetiology.

	Age (Years)	Author	Operation	Result	Aetiology
1	2	Herzog (1929)	None. Vomited roundworm terminally	Died 22 hr. after onset	? Roundworm
2	Boy, 2½	Gallie and Brown (1924)	Laparotomy. Vomited roundworm	Recovered	? Roundworm
3	Boy, 3	Holzmann (1927)	Laparotomy	Died	None found
4	Girl, 3	Mackenzie (1930)	None	Died	Had tonsillitis. ? Embolic sepsis
5	Girl, 4	Anderson (1923)	None	Died	None found
6	Boy, 5	Desjacques (1932)	Laparotomy	Died	None found
7	Boy, 7	Hagedorn (1913)	Laparotomy	Recovered	Trauma
8	7	Phélip (1920)	Laparotomy	Died	None found
9	Boy, 10	Dietrich (1932)	Laparotomy	Recovered	Trauma
10	Girl, 11	Foged (1932)	Laparotomy	Died	None found
11	Girl, 12	Novis (1923)	Laparotomy. 2 roundworms recovered from chest	Recovered	Roundworm
12	Girl, 12	Dobrotvinsky (1913)	Laparotomy	Recovered	Trauma
13	Girl, 13	Vogel (1924)	Laparotomy	Died	? Congenital abnormality
14	Girl, 13	Sebening (1925)	Stone removed from ampulla	Recovered	Cholelithiasis
15	Girl, 12½	Dobbs (1935)	Laparotomy and drainage	Recovered	? Embolic sepsis from mastoid ? Trauma
16	Girl, 3	Ger (1954)	Laparotomy only	Recovered	?
17	Boy, 6	Boss (1955)	Laparotomy and drainage	Died	? Valve in pancreatic duct
18	Girl, 4½	Haigh	Laparotomy	Recovered	?
19	Boy, 4	Haigh	Laparotomy	Recovered	?

Except Ger's and Boss's cases there is little biochemical information on any of these.

Discussion

Aetiology. A mild pancreatitis occurs as a complication of mumps in about 2·5% of cases according to Harries and Mitman (1947) but is rarely severe and only one fatality is recorded (Lemoine and Laparset, 1905). Occasionally diabetes mellitus results.

In the summary of all the recorded cases of acute haemorrhagic pancreatitis it is seen that trauma is an occasional but definite cause, as the cases of Hagedorn (1913) and Dietrich (1914) both occurred as a result of being run over by a cart wheel and that of Dobrotvinsky (1913) followed a severe blow in the epigastrium. Incidentally each of these three cases survived.

Roundworm infection seems blameworthy also, as both Herzog's (1929) and Gallie and Brown's (1924) patients vomited roundworms while Novis (1923) operated and removed two worms from the pancreatic duct in his girl. Rigby (1923) and others have reported pancreatitis in adults with roundworms in the pancreatic duct.

Sebening (1925) found a gall stone impacted in the ampulla of Vater in his 13-year-old girl which conforms with the aetiology sometimes found in adults.

Lesions of acute pancreatitis have also been found at necropsy in cases of septicaemia, and possibly the patients of Dobbs (1935), who had a cerebral abscess, and of Mackenzie (1930) with a follicular tonsillitis, come into the same general group caused by septic embolism.

This leaves about half the recorded cases which do not fit in with the above pathologies and any other definite aetiology.

Forshall and Rickham (1954) have shown that acute cholecystitis, which is also relatively uncommon in children, is frequently associated with a valve-like structure situated in the cystic duct. The valve-like structure just before the ampulla in the main pancreatic duct reported by Boss (1955) may therefore be of considerable significance, as more careful dissection or serial sections of some of the other post-mortem specimens might well have revealed similar lesions.

Acute pancreatitis has also been found at necropsy in severe burns in children collapsing suddenly and dying during the second and third week, but it is

part of a definite symptom complex and it is being recorded elsewhere.

Diagnosis. Most of the cases show a typical picture of the sudden onset of acute epigastric pain with profuse persistent vomiting, a silent distending abdomen and evidence of increasing intraperitoneal effusion, with guarding or rigidity and tenderness in the epigastrium. In two cases a cyanotic hue was noticed around the umbilicus but none record Grey Turner's sign of discoloration of the left loin.

A straight upright abdominal radiograph will help to exclude a perforated peptic ulcer by the absence of air under the diaphragm. Sugar is frequently found in the urine and the blood sugar level is usually raised above the upper limit of normal. Loewi's test is probably unreliable.

Markedly raised serum amylase and urinary diastase tests are the only certain confirmation of the diagnosis of acute pancreatitis.

Treatment. Of the cases reported the mortality rate is around 50% and all the survivors had a laparotomy performed. This may be the evidence on which Moncrieff and Evans (1953) state that without surgical intervention the outcome is always fatal, and Barrington-Ward (1937) advised drainage of the lesser sac. However, only three of the cases did not have a laparotomy and that was because they succumbed too precipitously. Three of the four cases occurring in the last decade all had laparotomy without definitive surgery and survived. This is probably a true estimate of the lower mortality rate likely with the improved standards of intravenous therapy and biochemical control to combat the severe surgical shock which develops so rapidly in this condition.

There is no justification for drainage of the biliary system in children and little theoretical good can be imagined from drainage of the lesser sac. Consequently, in line with the present therapeutic trend in adults, it would seem wiser, if the diagnosis has been definitely established, to treat conservatively with antibiotics, intravenous infusion, gastric suction and antispasmodics.

Summary

Seventeen cases of acute haemorrhagic pancreatitis in children have been recorded previously in the literature and two more are described.

Trauma and roundworm infestation are the two main established causes. Coincident biliary disease is rare and in over half the cases the cause is unknown, but valves in the pancreatic duct may be a cause possibly overlooked.

Contrary to the older teaching, if the diagnosis is established conservative treatment is advocated.

I wish to thank Miss Isabella Forshall and Mr. P. P. Rickham for allowing me to treat and publish these cases.

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SYMPTOMATIC PANCREATIC HETEROTOPIA OF THE PYLORUS ASSOCIATED WITH BILATERAL RENAL CORTICAL NECROSIS IN AN INFANT

BY

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(RECEIVED FOR PUBLICATION MARCH 27, 1956)

It has been suggested that islets of heterotopic pancreatic tissue are sometimes of clinical importance in adults, and that, occurring in the stomach wall, they may produce symptoms of pyloric spasm (Faust and Mudgett, 1940; Krieg, 1941; Waugh and Harding, 1946). They have been noted occasionally in infancy, but symptoms have not been attributed to them (Branch and Gross, 1935; Craig, 1955). Their importance will obviously vary with their size and position, and probably, with the intrinsic irritability of the neuromuscular apparatus of the gut. Even at necropsy the condition could easily be overlooked, and the present case in a 14-weeks-old boy suggests that it should be considered in the search for an organic basis for persistent vomiting in early infancy.

A heterotopia occurs when tissue elements proper to one area of the body develop at some other site where they are not normally found. Heterotopias are relatively common, especially throughout the intestinal tract. Thus gastric glands may be found in the oesophagus, and either gastric glands or pancreatic tissue, or both, are often found in congenital diverticula and in enterogenous cysts. Heterotopias may show disproportion in the relative proportion of their constituent tissues, and this is especially so in pancreatic heterotopias, where duct elements often greatly predominate over acinar tissue. However, they can usually be separated easily from hamartomata. In these some tissue constituents, such as vascular channels, nerve tissue, bone or cartilage, though normal for the area, are excessive, are disproportionate to other elements, and form respectively angiomatous tumours, neurofibromatous nodules and osteochondromata and other defects of bone modelling.

Clinical History

This full-term boy weighed 7 lb. 8 oz. (3,400 g.) at birth. Delivery was normal and one previous child is alive and well aged 3 years.

He was admitted to hospital on the seventeenth day of life with projectile vomiting, which started on the tenth day, and with loss of weight. There was visible peristalsis and a palpable tumour in the epigastrium and four-hour retention of a barium meal. Three days later operation revealed a hard firm tumour at the pylorus described as typical of hypertrophic pyloric stenosis and Rammstedt's operation was done. He was discharged seven days later after an uneventful recovery.

Three days later he vomited again with green diarrhoea and was in hospital for two days. Ten days later at the age of six weeks, he was again admitted for vomiting and diarrhoea. No intestinal pathogens were isolated, vomiting ceased after 48 hours and he gained 9 oz. (250 g.) in 12 days in hospital.

At the age of 10 weeks he weighed 11 lb. (5,000 g.) but at 12 weeks he was readmitted for diarrhoea. Intestinal pathogens were not isolated, and three days later vomiting developed and he rapidly became dehydrated. Saline infusions were given. The vomitus was coffee ground and on the fifth and sixth days he passed tarry stools. The haemoglobin was only 55% and he was transfused with 200 ml. blood but without clinical improvement. Despite treatment of a stomatitis he became reluctant to feed, most of his feeds were vomited and the vomitus continued to contain altered blood. He died two weeks after admission aged 14 weeks.

Necropsy

The body was that of an emaciated male infant. Externally there was no congenital defect, no abnormal pigmentation and no oedema. The surgical incision was healed.

The thymus is atrophic, the lungs are slightly collapsed, reddish, and, though oedematous posteriorly, they are not consolidated. The great vessels enter and leave the heart normally and there is no abnormality of the valves or cardiac septa. There is no hiatus hernia and the position of the cardio-oesophageal junction in relation to the intact diaphragm is normal.

There are no abnormal peritoneal adhesions. The stomach is empty and is not dilated. The pyloric region is slightly hypertrophied, but the muscle is relaxed and soft and the canal admits a probe normally. Only the

posterior quadrant shows distinctive thickening of the muscle wall extending proximally for 1 cm. from the pylorus. There is patchy congestion of the mucosa of the lesser curve near the cardia, but elsewhere it is pale and no ulcers or erosions can be found.

Apart from the kidneys the other organs show only some generalized atrophy. The kidneys are not recognizably enlarged, but externally and, even through their capsules, they appear unduly congested and dark in colour, with irregular areas of reddish-yellow mottling. On section the cortex shows a pale yellowish zone which occupies the outer one-third to one-half of the cortex. This is discontinuous and of irregular outline, but about two-thirds of the whole subcapsular zone is involved. A thin red line separates it from the capsule. It is bounded by a narrow irregular zone of deeply congested kidney tissue and, though firm, appears entirely structureless. The remainder of the kidney is congested, but otherwise the inner part of the cortex and the whole of the medulla show their normal pattern and the veins of the boundary zone and the radicles of the renal veins are free of thrombi. The pelves and ureters are normal.

The meninges are unthickened and free of haemosiderin. The brain externally, and on section after fixation, is normal.

Histological Examination

Routine sections have been prepared from all organs and multiple sections from all four quadrants of the pylorus and from the kidneys. The routine sections show only terminal congestion and oedema of the lungs. The sections from the posterior quadrant of the pylorus show pancreatic tissue in the submucosa and in the circular and longitudinal muscle layers. Pancreatic acini and a grossly disproportionate number of pancreatic ducts are present. The acini appear inactive and the ducts are dilated and have a prominent mantle of somewhat immature connective tissue around them. Islet tissue is not present. Multiple sections show no ulceration of the overlying gastric mucosa. Numerous pancreatic ducts traverse the submucosa and must open separately into the stomach.

In the kidney there is widespread and gross congestion affecting both glomeruli and small inter-tubular capillaries. This is especially marked around the necrotic areas and extends into them. The necrosis extends to the renal capsule though in some tubules immediately deep to the capsule isolated groups of cells survive. Towards the periphery of the necrotic tissue shrunken nuclei persist, the red blood cells retain their haemoglobin and there are some polymorphs. In relatively small areas towards the centres of the necrotic areas only the outline of shrunken tissue is recognizable. Tubules lying in the cortex deep to the necrotic zone and in the medulla show little abnormality, though collecting tubules often contain haemoglobinuric casts. The blood vessels within the necrotic areas show necrosis of their wall and fibrin and breaking-down blood cells in their lumen, but outside the areas of necrosis the blood vessels are normal and there are no ante-mortem thrombi.

Discussion

It is not possible to determine whether this was a case of pyloric pancreatic heterotopia and congenital pyloric stenosis, or whether the apparent thickening of the pylorus seen at operation was due only to a strong reflex spasm of its musculature secondary to the heterotopic tissue. The division of some muscle fibres probably reduced, or abolished for a time the reflex spasm. When pancreatic heterotopias have caused symptoms they have rarely, if ever, done so directly by virtue of their size, but only by reflex disturbance of intestinal movement. Other factors, such as minor intestinal upsets, will influence the irritability of the bowel and symptoms may be expected to vary considerably from time to time.

Pancreatic heterotopias in the region of the pylorus have been mentioned occasionally in early infancy as an incidental finding (Branch and Gross, 1933; Craig, 1955). One of us (J.E.M.) has for some years included a section through the pylorus in the routine histology of his own and supervised necropsies on stillbirths, newborn babies and young infants. In this material, comprising over 500 cases, no other heterotopias have been encountered at this site. Heterotopias are congenital malformations present from birth. Routine inspection and one section might readily fail to reveal a small heterotopia. However, from this material there is no reason to suppose that the incidence of heterotopias in this area is higher than the 1 in 400 individuals suggested by Waugh and Harding (1946) from a review of the literature. Again, it may be emphasized that symptoms are probably produced in a few cases only. Heterotopias are commonest in the submucosa, where they probably produce little disturbance of neuromuscular activity. Again factors concerned with the irritability of the bowel are probably involved, since in the recorded cases symptoms apparently developed only in adult life though the condition must have been present from birth.

Blood loss into the intestine, suggested by the tarry stools, probably cannot be attributed directly to the heterotopia. Minute acute erosions in the stomach mucosa, commonest in the fundus and body, are extremely difficult to recognize as ante-mortem lesions at necropsy. They are non-specific and relatively common. Study of the mucosa over the heterotopia showed it was proper to the stomach and free of ulceration. Even in illness some acid secretion by the stomach is likely to persist as long as any secretion from the heterotopic pancreatic tissue, and it is difficult to appreciate how such a heterotopia could produce gastric ulceration by its enzyme secretion.

The occurrence of bilateral cortical necrosis of the kidneys is of considerable interest. This condition has been described, and the theories of its origin discussed in detail, in the monograph of Sheehan and Moore (1952). Cortical necrosis may or may not be due to spasm of small blood vessels and the present case contributes nothing new to the discussion of the aetiology of the condition. Comparison with adult cases suggests that the small kidney of the infant is less rigid than that of the adult, and that congestion and even haemorrhage tends to be more marked. The recognition of different zones in the necrotic tissue is even more arbitrary than in the adult. The survey of Sheehan and Moore and the paper by Campbell and Henderson (1949) show that cortical necrosis is rarely described in infancy and childhood. This is true for the fully developed condition, but study of routine sections from cases of gastro-enteritis in infancy suggests that small focal areas of tubular necrosis occur not infrequently. In fresh and relatively well fixed material the focal change in the parenchymatous tissue appears distinctive, but it is difficult in these small and relatively terminal lesions with their scanty or absent interstitial reaction to produce satisfactory evidence that they are, indeed, ante-mortem lesions.

The lesions of cortical necrosis are entirely different from those of renal venous thrombosis (Morison, 1945). The tendency to involve the more immediately subcapsular portion of the cortex instead of the medulla and deeper cortex, and the absence of thrombi in vessels beyond the involved area is distinctive, even apart from the absence of thrombi in the veins of the boundary zone.

Summary

A pancreatic heterotopia involving the circular and longitudinal muscle of the posterior quadrant of the pyloric antrum in a male infant is described. An operation for hypertrophic pyloric stenosis was performed on the 20th day of life. Symptoms returned after 10 days and, until death at the age of 14 weeks, he had frequent episodes of vomiting and diarrhoea.

Influences increasing the intrinsic irritability of the bowel are probably always important as an additional factor, but in some cases of persistent vomiting the primary factor may be reflex spasm from such a lesion.

Circulatory failure developed and bilateral cortical necrosis of the kidney was found. The lesions resulting from this are entirely distinct from those of renal venous thrombosis.

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PATENT DUCTUS ARTERIOSUS

A REVIEW OF 108 CASES TREATED SURGICALLY

BY

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(RECEIVED FOR PUBLICATION APRIL 5, 1956)

Surgical closure of a patent ductus arteriosus was first reported by Gross and Hubbard in the year 1939. Since then the procedure has been attempted in thousands of cases with a mortality rate in the larger published series of from 0 to 2% (Gilchrist, 1948; Sellors, 1948; Potts, Gibson, Smith and Riker, 1949; Scott, 1950; Gross, 1952; Starer, 1953; Tubbs, 1955). Simple ligature of the ductus has in some cases failed to achieve complete obliteration of its lumen and in others has been followed by recanalization. Gross therefore in 1947 adopted the practice of dividing the vessel and many surgeons now follow his example, especially when dealing with a large ductus.

We have reviewed the first 108 children between the ages of 1 and 16 years referred to one of us (J.D.H.) with a patent ductus arteriosus and treated surgically by Mr. F. Ronald Edwards and Mr. B. J. Bickford, and have attempted to assess not only the results of operation and their bearing upon the choice of surgical procedure, but also the value of the various diagnostic criteria of this condition. We have excluded infants under the age of 1 year because they present special problems in diagnosis and treatment.

The patients were referred by other consultants, school medical officers and family doctors and are probably representative of children seen in other centres with patent ductus arteriosus during the period under review, 1949 to 1953. The series will probably differ, however, from more recent groups in including a larger proportion of older children for whom surgical treatment did not become available until they were in their 'teens.

Findings

Of the 108 patients, 84 (78%) were girls. Four cases were complicated by coarctation of the aorta of mild degree, unassociated with clinical evidence of the condition and insufficient to warrant resection, one by a ventricular septal defect and one by congenital heart block.

The symptoms, physical signs, radiological and electrocardiographic findings are summarized in Table 1.

Symptoms. Excessive dyspnoea on exertion, undue fatigue, recurrent respiratory infections or failure to thrive were noted in 40 cases (37%).

Physical Signs. Of the physical signs, the typical Gibson murmur was the most constant and best heard in the second left intercostal space, continuous throughout the cardiac cycle, with late systolic accentuation and a rattling 'machinery' quality. It was heard in 97 (95%) of the patients.

In 11 cases the murmur was atypical. In four of these it was blowing rather than rattling. In three of the four the ductus was small with an external diameter of 4·5 mm. or less and in the fourth the diameter was 9 mm. In the remaining seven the diastolic element was soft and confined to early diastole. In these cases there was marked pulmonary hypertension, demonstrated by cardiac catheterization in five and at operation in two. This complication is known to cause a reduction in blood flow through the ductus and consequently an alteration in the character of the murmur.

A thrill was felt in 79 cases (73%), continuous in 32 (30%), systolic only in 47 (43%).

The second heart sound in the pulmonary area is so loud in many children with normal hearts that it is often difficult to know if it is within the limits of normal or not. In the seven patients with pulmonary hypertension, however, it was definitely accentuated. In some cases the sound was obscured by the Gibson murmur. Splitting was usually heard, but with pulmonary hypertension it was occasionally single, due presumably to synchronous closure of the pulmonary and aortic valves.

A mid-diastolic murmur was heard in the mitral area in many of the cases, more frequently in those

TABLE 1

SYMPTOMS, PHYSICAL SIGNS AND RADIOLOGICAL AND ELECTROCARDIOGRAPHIC FINDINGS

Case No.	Age (in years)	Ductus Diameter (mm.)	Symptoms	Murmur	Thrill	Apical Diastolic Murmur	Collapsing Pulse	Blood Pressure (mm. Hg)		Radiological C/T Ratio		Electrocardiogram				Surgical Closure	Pulmonary Hypertension
												L.V. Dominance Sv_1+Rv_6 mm.		R.V. Dominance Rv_1 mm.			
								Pre-operatively	Post-operatively	Pre-operatively	Post-operatively	Pre-operatively	Post-operatively	Pre-operatively	Post-operatively		
1	11 9/12	W.	+	T.	S.	−	−	110/50	115/80	55	41	St.	St.	St.	St.	P.	−
2	12 5/12	10	+	T.	C.	−	+	118/58	120/75	59	55	St.	St.	St.	St.	I.	−
3	11 7/12	W.	−	T.	C.	−	+	118/42	105/55	47	48	St.	St.	St.	St.	I.	−
4	5 7/12	?	+	T.	C.	−	+	120/50	120/70	64	54	St.	St.	St.	St.	I.	−
5	4 4/12	6	−	T.	S.	−	−	84/48	105/80	−	51	St.	St.	St.	St.	P.	−
6	14 3/12	W.	S.	T.	S.	−	+	110/45	128/80	57	56	St.	St.	St.	St.	I.	−
7	6 4/12	8	+	T.	S.	−	−	104/55	102/72	55	47	St.	St.	St.	St.	P.	?+
8	5 10/12	8	D.	T.	S.	−	−	84/44	110/78	50	53	St.	St.	St.	St.	P.	−
9	7	8	−	T.	C.	−	−	74/34	82/48	St.	St.	St.	St.	St.	St.	P.	−
10	7 4/12	4	−	A.	−	−	−	100/60	100/70	50	46	−	−	−	−	P.	−
11	6 10/12	3	−	A.	S.	−	−	93/38	90/50	50	46	St.	St.	St.	St.	P.	−
12	5 5/12	W.	+	T.	S.	−	−	110/50	115/80	55	41	St.	St.	St.	St.	P.	−
13	7 4/12	6	−	T.	C.	−	+	118/57	120/75	59	55	St.	St.	St.	St.	P.	−
14	6	6	+	T.	C.	−	+	118/42	105/55	47	48	St.	St.	St.	St.	P.	−
15	5 6/12	4	+	T.	−	−	−	102/60	110/80	54	52	St.	St.	St.	St.	P.	−
16	8 5/12	5	−	T.	S.	−	+	90/58	105/60	49	50	St.	St.	St.	St.	P.	−
17	6 4/12	5	+	T.	C.	−	+	—	105/70	54	51	St.	St.	St.	St.	P.	−
18	5 2/12	6	−	T.	C.	−	−	115/45	115/75	52	45	St.	St.	St.	St.	P.	−
19	12 10/12	10	−	T.	S.	−	−	130/70	116/75	46	44	St.	St.	St.	St.	P.	−
20	11 1/12	15	+	T.	S.	+	+	112/40	115/60	65	58	St.	St.	St.	St.	I.	+
21	10 3/12	5	−	T.	C.	−	−	130/70	110/70	49	55	St.	St.	St.	St.	P.	−
22	7 5/12	8	+	T.	−	−	+	125/70	110/70	50	48	St.	St.	St.	St.	P.	−
23	4 7/12	6	−	T.	S.	+	+	90/45	90/60	55	52	45	29	9	9	P.	?+
24	6 8/12	7	D.	T.	S.	+	+	124/54	—	—	—	—	—	—	—	P.	−
25	12 2/12	9	+	A.	−	−	−	104/60	115/80	54	49	St.	St.	St.	St.	P.	−
*26	4 10/12	9	−	T.	S.	+	+	95/40	105/70	64	58	57	55	6	5	P.	−
27	4 8/12	8	−	T.	S.	+	+	130/55	110/65	59	59	59	59	10	8	R.	−
28	3 11/12	5	−	T.	−	−	−	104/70	115/80	59	51	31	27	6	7	P.	−
29	5 7/12	9	−	T.	S.	+	+	138/54	120/85	63	48	50	29	8	4	I.	?+
30	9 5/12	7	−	T.	S.	−	−	114/78	105/80	53	45	56	36	5	10	P.	−
31	6 10/12	13	+	A.	S.	+	+	115/35	102/60	64	50	86	50	15	9	R.	+
32	10 9/12	12	+	T.	C.	+	+	130/40	115/60	55	43	56	36	16	16	P.	−
33	5 11/12	5	−	T.	S.	+	+	112/60	110/70	51	51	26	23	10	10	P.	−
34	8 8/12	15	+	T.	S.	+	+	95/40	88/65	64	56	74	26	17	4	I.	−
35	5 5/12	12	+	T.	C.	+	+	110/35	110/70	60	51	50	32	22	22	P.	−
36	14 3/12	5	−	T.	−	−	+	120/65	110/70	51	46	47	37	6	7	P.	−
37	15 11/12	6	−	T.	−	−	+	130/75	120/70	44	43	19	20	10	10	P.	−
38	10 2/12	6	D.	T.	−	−	−	125/66	124/70	46	47	52	33	9	7	P.	−
39	4 11/12	6	+	T.	−	−	−	115/60	100/65	53	53	26	23	9	10	P.	−
40	10 9/12	7	+	T.	−	−	+	100/50	120/70	56	50	32	20	10	5	P.	?+
41	3 3/12	9	D.	T.	C.	+	−	90/55	110/70	59	55	40	21	10	6	P.	?+
42	7 6/12	6	−	T.	−	−	+	125/75	114/75	52	49	35	33	5	5	P.	−
43	3 3/12	6	−	T.	C.	−	+	—	98/62	57	52	22	12	12	9	P.	?+
44	6	8	−	T.	+	+	+	100/45	102/60	51	47	44	37	17	15	R.	?+
45	4 5/12	5	+	T.	−	−	−	110/65	115/62	—	—	26	15?	10	5?	P.	−
46	9 8/12	8	−	T.	−	−	+	125/65	120/80	48	48	16	14	3	2	P.	=
47	11 9/12	11	+	T.	−	−	−	90/60	118/75	50	49	40	40	7	7	P.	−
48	3 2/12	7	D.	T.	S.	−	+	112/60	98/70	56	51	33	33	10	13	P.	?+
49	3 7/12	10	−	T.	−	−	+	100/40	98/70	64	59	62	34	18	10	P.	−
50	2 11/12	8	−	T.	S.	−	+	110/50	110/85	58	52	52	35	20	15	P.	−
51	7 9/12	15	+	A.	−	−	−	82/60	—	56	—	17	—	16	—	Ab.	+(100/70)
52	3	8	−	T.	S.	+	+	130/70	105/65	60	54	33	23	7	5	P.	−
53	4 8/12	9	D.	T.	S.	+	−	95/75	110/60	50	49	17	20	3	2	P.	−
54	3 5/12	10	−	T.	+	+	−	95/40	—	60	—	30	30	12	21?	P.	+ (75/55)
55	3 3/12	6	+	T.	S.	−	−	110/75	102/70	—	—	30	28	22	20	P.	−
56	3 2/12	7	D.	T.	+	+	+	108/50	115/70	58	54	45	32	9	10	P.	−
57	5 7/12	6	D.	T.	S.	+	+	100/75	98/72	51	51	37	23	9	8	P.	−
58	6 4/12	8	+	T.	C.	+	−	90/55	94/60	—	—	23	21	3	3	P.	−
59	6 5/12	6	+	T.	−	−	−	110/60	116/68	57	56	25	27	10	7	P.	−
60	5 7/12	?	+	T.	+	−	+	135/60	122/86	60	49	43	30	8	5	P.	−
61	9 1/12	11	+	T.	C.	+	+	115/55	116/80	59	54	49	33	10	10	R.	−
62	2 2/12	8	−	T.	S.	−	+	90/40	100/70	60	54	41	20	9	8	P.	−
63	3 9/12	5	+	A.	−	−	+	98/55	93/60	59	49	26	22	10	10	P.	−
64	5 9/12	7	−	T.	S.	+	+	95/55	114/70	55	49	50	31	9	5	P.	−
65	10 9/12	8	D.	T.	C.	+	−	100/70	98/80	51	48	43	36	6	5	P.	−
66	7 6/12	6	D.	T.	−	−	+	120/65	110/80	47	41	23	22	6	5	P.	−
67	4 10/12	8	D.	T.	−	−	+	105/60	100/70	53	51	26	19	5	3	P.	−
70	9	8	−	T.	−	−	−	100/60	98/60	52	44	14	10	10	10	P.	−

TABLE 1—*continued*

Case No.	Age (in years)	Ductus Diameter (mm.)	Symptoms	Murmur	Thrill	Apical Diastolic Murmur	Collapsing Pulse	Blood Pressure (mm. Hg.)		Radiological C/T Ratio		Electrocardiogram				Surgical Closure	Pulmonary Hypertension
												L.V. Dominance Sv_1+Rv_6 mm.		R.V. Dominance Rv_1 mm.			
								Pre-operatively	Post-operatively	Pre-operatively	Post-operatively	Pre-operatively	Post-operatively	Pre-operatively	Post-operatively		
71	9 11/12	6	D.	T.	C.	−	+	120/50	106/68	46	44	46	36	6	5	P.	−
72	3 3/12	9	D.	T.	C.	+	+	115/38	115/75	63	55	30	18	6	5	P.	−
73	7 10/12	8	−	T.	C.	+	−	100/65	116/72	50	50	41	33	6	5	P.	−
74	3 5/12	16	+	A.	S.	+	−	90/50	100/55	62	59	38	—	8	—	I.	+
75	5 4/12	7	D.	T.	C.	−	−	110/75	100/65	53	55	50	39	10	8	P.	−
76	2 10/12	9	−	T.	C.	+	−	110/50	90/66	62	59	65	45	10	10	P.	−
76A	5 5/12	6	−	T.	S.	−	+	100/35	94/54	54	52	39	39	4	5	P.	−
65B	1 1/12	8	+	T.	C.	+	−	145/55	—	61	51	41	—	14	—	P.	−
77	5 8/12	6	+	T.	C.	+	+	110/5	105/65	50	48	18	15	4	5	P.	−
78	2 9/12	8	D.	T.	S.	−	−	100/60	105/60	57	54	21	20	4	6	P.	−
79	9 11/12	7	+	T.	C.	−	−	140/75	138/88	47	47	38	27	3	2	P.	
81	14 1/12	11	−	T.	C.	−	−	150/70	130/80	57	49	40	32	1	1	P.	−
82	5 10/12	?	D.	T.	C.	−	−	92/56	98/68	55	55	24	20	10	7	P.	−
83	13 6/12	7	D.	T.	S.	−	−	125/75	120/80	49	46	25	—	2	—	P.	−
*84	3 11/12	10	−	T.	+	−	+	125/45	118/80	67	55	52	25	4	8	P.	−
85	13 5/12	11	+	T.	S.	+	+	94/48	115/85	54	44	46	40	1	1	P.	−
86	5 8/12	4	−	T.	S.	−	+	102/64	112/65	56	50	29	28	2	2	P.	−
87	5 8/12	7	D.	T.	S.	−	+	102/50	104/60	54	54	46	33	3	3	P.	−
88	7	10	+	T.	S.	+	+	105/85	110/85	63	—	52	—	5	—	P.	+ (100/60)
89	4 2/12	6	−	T.	S.	−	+	117/60	110/82	54	58	26	30	6	12	P.	−
90	4 6/12	6	−	T.	S.	−	−	115/65	110/70	59	56	32	28	4	5	P.	−
90A	9 5/12	7	−	T.	S.	+	+	125/64	135/75	51	49	34	32	5	5	P.	−
91	3 4/12	5	D.	T.	−	−	+	110/64	100/55	51	56	27	—	7	—	P.	−
94	2 1/12	14	+	A.	S.	+	−	80/?	90/65	65	62	41	27	13	13	I.	−
95	5 11/12	5	−	T.	−	−	+	120/65	120/80	57	54	26	—	8	7	P.	−
96	6 1/12	5	−	T.	−	−	−	110/76	118/80	49	51	29	29	2	3	P.	−
97	7 6/12	5	+	T.	S.	+	−	120/70	88/70	42	43	24	—	10	—	P.	−
98	5 6/12	8	+	T.	S.	+	+	115/50	120/80	61	60	45	—	8	—	P.	−
99	6 6/12	16	−	A.	S.	+	−	115/68	—	59	—	36	—	7	—	Ab.	+ (64 mean)
101	4	10	+	A.	S.	+	+	115/55	110/80	67	60	22	—	9	—	P.	+ (82/47)
102	1 11/12	14	+	A.	S.	+	+	115/?0	110/70	70	63	26	26	5	5	I.	+ (76/42)
103	1 3/12	7	D.	T.	S.	−	−	110/55	—	58	58	St.	St.	St.	St.	P.	−
104	5 10/12	9	D.	T.	−	−	−	93/50	110/60	57	48	20	—	1	—	P.	−
106	5 6/12	7	+	T.	−	−	−	85/60	110/80	59	51	25	—	8	—	P.	−
107	4 11/12	7	−	T.	C.	+	−	116/68	110/70	54	54	37	—	2	—	P.	−
108	5 10/12	7	−	T.	C.	+	−	116/58	120/65	61	60	33	30	2	2	P.	−
*23/1	11 9/12	10	−	T.	C.	−	−	105/45	115/85	60	57	St.	St.	St.	St.	P.	+
*23/2	4 2/12	6	+	T.	−	+	−	105/70	95/65	54	55	43	28	9	5	P.	−
*23/3	2 9/12	10	−	T.	S.	+	+	120/58	102/60	58	53	47	27	15	15	P.	+
*23/4	2 11/12	10	−	T.	C.	−	−	105/55	110/82	61	—	42	St.	2	St.	P.	−

T=typical machinery murmur, A.=atypical murmur, C.=continuous, S.=systolic, St.=standard leads 1, 2, 3, P.=permanent, R.=recurrence, I.=incomplete, Ab.=abandoned, D.=doubtful, being retrospective, W.=wide.

* Associated abnormality: 26, congenital heart block; 84, ventricular septal defect; 23/1, 23/2, 23/3, 23/4, slight coarctation of aorta.

seen later in the series. It was recognized only once in the first 20 patients but was heard in 53 of the remaining 88, and this latter proportion probably represents its true incidence.

The pulse was described as 'collapsing' in 53 cases (49%). In many normal children the diastolic fall of pressure is rapid and the pulse more collapsing than in an adult. It is therefore in some cases difficult to decide if it is abnormally collapsing or not. One would expect this difficulty to be less when the pulse pressure is large, and Table 2 demonstrates that the higher the pulse pressure the larger was the percentage of pulses recorded as collapsing.

TABLE 2
PULSE PRESSURES RELATED TO COLLAPSING PULSE

Pulse Pressure (mm. Hg)	Collapsing Pulse	Total
40 or less	7 (23%)	30
41–50	11 (46%)	24
51–60	16 (53%)	30
61–70	8 (80%)	10
71 and over ..	9 (75%)	12
	51 (49%)	106

Two cases are omitted as the blood pressure readings before operation were unsatisfactory.

Radiographs. For the analysis of the radiological findings we are indebted to Dr. J. K. Walker. He

first estimated the size of the heart by means of the cardio-thoracic ratio. Taking the upper limit of normal to be 52%, he found evidence of cardiac enlargement in 70% of cases. Although this ratio is not a completely satisfactory measure of the actual size of the heart it does offer a simple and reasonably accurate method of comparing heart size at different times in the same individual, and it will be seen from Table 3 that the cardio-thoracic ratio tended to increase with the diameter of the ductus found at operation.

TABLE 3
RELATION OF CARDIO-THORACIC RATIO TO SIZE OF PATENT DUCTUS

Cardio-thoracic Ratio (%)	Patent Ductus Arteriosus up to 7 mm. Diameter	Diameter 7·5-10 mm.	Diameter 10 mm. and Over
52 or less ..	22 (46%)	7 (21%)	1 (7%)
53–56	16 (33%)	4 (12%)	3 (21%)
57–60	8 (16%)	13 (40%)	4 (28%)
61–64	3 (6%)	7 (21%)	3 (21%)
65 or over ..	—	2 (6%)	2 (14%)
Total ..	49	33	13

He then applied Meyer's more accurate method of diagnosing enlargement of the heart, in which the cardiac area is calculated from the long and broad diameters of the heart in the postero-anterior film and compared with the cardiac area of a normal child of similar height and weight (Meyer, 1949). By this means, cardiac enlargement was suggested in 74% of the patients.

It is possible that if we had used Lind's method of calculating the cardiac volume we would have found that there was some increase in volume in a still higher proportion of cases (Lind, 1950). The left ventricle appeared to be enlarged in 86 cases (81%), the pulmonary arc unduly prominent in 93 (87%), the hilar vessels enlarged in 95 (89%) and the lung fields hyperaemic in 97 (91%). Expansile pulsation of the hilar vessels was detected in 27 cases (25%).

Electrocardiographs. All but two patients were electrocardiographed. In 23 of the early cases the standard leads only were employed but in the other 83, aVR, aVL, aVF, V_1, V_3, V_6 and latterly V_{3R} were also recorded. The electrocardiograph (E.C.G.) was normal in 42 of the 83 cases. A considerable number, however, showed changes which are regarded by some authors (Sodi-Pallares and Marsico, 1955; Landtman, 1954) as indicative of left ventricular dilatation, namely, excessive amplitude of R_{V6} and S_{V1}, the sum of the two exceeding 35 mm., together with a tall upright T_{V6}. In 33 of the 83 patients (40%), the above criteria of left ventricular dilatation were found. In a further two, excessively tall R waves with inverted T waves in lead V_6 suggested left ventricular hypertrophy rather than dilatation (Landtman, 1954).

Evidence of right ventricular hypertrophy, namely, R_{V1} greater than 10 mm. (Switzer and Besoain, 1950), was found in 14 cases. In four it occurred without evidence of left ventricular hypertrophy or dilatation. In two of these, a pulmonary artery pressure almost at systemic level suggested that the shunt might soon have become reversed, and in one such reversal was in fact seen under the conditions of thoracotomy. In the other two, with R_{V1} equalling 10 and 13 mm. respectively, significant pulmonary hypertension was not noted at operation, and the ductus, 6 mm. in diameter in each, was of a size not usually accompanied by this complication. In an additional case without pulmonary hypertension, R_{V1} of 10 mm. and S_{V6} of 14 mm. also satisfied Orme's criteria for right ventricular hypertrophy (Orme and Adams, 1952). In the remaining 10 cases evidence of right ventricular hypertrophy was accompanied by that of left ventricular hypertrophy or dilatation. In only seven of these was there definite evidence of pulmonary hypertension at operation or on cardiac catheterization. In the other three, with R_{V1} 20, 15 and 14 mm. respectively, there was no obvious pulmonary hypertension and therefore possibly no right ventricular hypertrophy. On the other hand, the ductus was of moderate size, 8 mm. in diameter, in two of them, and large, 14 mm. in diameter, in the other, and it seems perhaps more probable that there was in all three a degree of pulmonary hypertension sufficient to have caused some right ventricular hypertrophy but not to have resulted in gross macroscopic changes in pulmonary vasculature by the time the operation was performed.

Cardiac Catheterization. Cardiac catheterization was only performed, first, in those cases in which there was any doubt about the presence of a patent ductus arteriosus after the physical signs and radiological and E.C.G. findings had been considered, or, secondly, when significant pulmonary hypertension was thought to be present. It was undertaken, therefore, when the murmur was atypical or very loud and accompanied by an unusually loud second sound, and sometimes also when radiographs showed marked hilar enlargement and a very large heart. It was, however, not available for many of the early patients whom we might have wished to investigate in this way and was employed in only seven. In all these, patency of the ductus was indicated by the demonstration of increased oxygenation of the blood in the

pulmonary artery and in three it was confirmed by passing the catheter through it into the aorta. Significant pulmonary hypertension was recorded in six; in the seventh the record was unsatisfactory but also suggested pulmonary hypertension. In one additional cyanosed patient the ductus was catheterized and the oxygen saturation of the blood from the aorta was shown to be reduced, indicating a right-to-left shunt from pulmonary artery to aorta. The child was, therefore, considered to be unsuitable for surgery and was excluded from this series.

Surgical Procedure. In each of the 108 patients thoracotomy was performed under anaesthesia with intravenous barbiturates, relaxants and nitrous oxide, and the diagnosis was confirmed. In 107, closure of the ductus was attempted. In 103 of these cases, double ligation with strong linen thread appeared to abolish the flow through the ductus. In three simple ligation was impossible owing to the great width of the vessel, 14-16 mm. diameter, and to the very high pressure within it. Partial closure was, however, effected by a pad tied firmly over the vessel which definitely reduced the shunt and resulted in an immediate diminution in heart size and a significant rise of diastolic pressure. Ligation of a high-pressure ductus was facilitated in some cases by the induction of hypotension by a ganglion-blocking agent such as 'arfonad'. In another patient brisk haemorrhage occurred during the dissection of a high-pressure sclerotic ductus and the operation was abandoned. There were no ill effects from this operation and the case is still under review. In the remaining case the shunt, which had been left to right during cardiac catheterization, was found to be reversed under the conditions of the operation and closure was not attempted. The patient died three days later. Necropsy was unfortunately not performed.

Results of Operation

Symptoms. In each of the 40 children who presented with symptoms operation was followed by definite improvement, and in a further 20 (18%) follow-up revealed that pre-operative limitation of activity had passed unnoticed by the patient's family, as increase in the child's exercise tolerance was noted by parents who had mistakenly considered his energy to have been normal before operation.

Physical Signs. These were considered as murmur and blood pressure readings.

MURMUR. In 92 of the 108 patients (85%) the diagnostic murmur was no longer audible after operation and did not recur during the follow-up period of at least six months. In many of these cases a systolic murmur persisted in the pulmonary area. It was usually soft and varied in intensity with respiration and was considered to be of no significance.

In seven patients, all with a patent ductus of 9 mm. or more in diameter, a continuous murmur was heard within two weeks of operation despite apparently satisfactory ligation. As dressings were not removed during the first few days to facilitate auscultation, it is not known if in some of these cases the murmur was audible immediately after the operation: in others it definitely did not develop until during the second week. In all seven, however, the diastolic blood pressure rose after operation by at least 15 mm. Hg and there was radiological evidence of a decrease in the size of the heart. In two of these cases the murmur ceased after about a year, indicating spontaneous closure, which may therefore still take place in the others. In four cases the Gibson murmur recurred one to 12 months after operation. In two of these the ductus has been retied and the murmur has ceased. The third refused a second operation and the fourth is still being considered for further surgery. In the three cases in which a pad was used to compress the ductus only partial closure was achieved and the continuous murmur persisted. In the remaining two patients, the one with the friable ductus and the other with the reversed shunt at operation, ligation was not performed.

BLOOD PRESSURE. The immediate effect of ligation of the ductus was a rise in the systolic and diastolic blood pressure. The systolic pressure fell again over the course of a week or so but the diastolic remained higher than the pre-operative level, being over 50 mm. Hg in all but two patients, whose pressure was 48 mm. Hg. The distribution of the diastolic blood pressures before and after operation is set out in Table 4.

TABLE 4
DIASTOLIC BLOOD PRESSURE BEFORE AND AFTER OPERATION

Pressure (mm. Hg)	Pre-operative	Post-operative
30 or less	2 (2%)	—
31–40	13 (13%)	—
41–50	22 (22%)	2 (2%)
51–60	30 (30%)	19 (19%)
61 and over ..	33 (33%)	79 (79%)
	100	100

(Cases 17, 24, 43, 51, 76B, 88, 99, 103 are omitted owing to inadequate data.)

Radiographs. The rise in the diastolic level of the systemic blood pressure with the abolition of the

aorta-pulmonary shunt might be expected to be paralleled by a reduction in the size of the heart. This was seen on *x*-ray examination in 79 patients (64%), including many in whom the radiological appearances before operation were considered to be within normal limits. The comparison between the pre-operative and post-operative radiographs could not be made in a certain number of cases for various reasons, such as incomplete follow-up, difference in positioning for radiography, etc. A film at an interval of three months was usually used for the post-operative study and any reduction in the cardio-thoracic ratio can therefore be assumed to be independent of general growth of the body relative to the heart. A reduction in the cardio-thoracic ratio at this interval has been interpreted as an indication of absolute reduction in the size of the heart. In Table 5 the distribution of the percentage reduction in the cardio-thoracic ratio is set out. The table only includes those cases in which the external diameter of the ductus was recorded and in which comparable pre-operative and post-operative radiographs were available, and it is excessively weighted with patients with small ductuses. It does, however, tend to confirm that ligation of a large ductus often leads to a considerable reduction in heart size. In films taken 18 months or longer after operation this reduction was in many cases even more marked.

TABLE 5
POST-OPERATIVE REDUCTION IN CARDIO-THORACIC RATIO

Ductus Diameter (mm.)	Cardio-thoracic Decrease Less than 4%	4–7% Decrease	8–11% Decrease	12% Decrease and Over	Total
4 or less	31	4	—	—	35
7·5–10	16	11	7	1	35
10·5 and over ..	5	2	3	2	12
	52	17	10	3	82

Electrocardiographs. A similar trend was seen in the E.C.G. records of the 35 cases showing left ventricular dilatation or hypertrophy before operation. Thirty had comparable post-operative records of which 24 were within normal limits, the sum of S_{V1} and R_{V6} being less than 35 mm., suggesting a decrease in the size of the left ventricle. One of the six, with a persistently abnormal E.C.G., had an associated congenital heart block and the persistent enlargement of the left ventricle may be due to the high stroke output necessitated by the slow rate. In another four cases the sum of S_{V1} and R_{V6} fell from 86 to 50 mm., 50 to 39 mm., 65 to 45 mm., and 46 to 40 mm. respectively, and in the final case there was no change in the pre-operative total of 39 mm., a figure only slightly above normal.

The T wave became smaller in V_6 in all but six cases, confirming a decrease in left ventricular dilatation, and upright in the two cases in which it was inverted before operation, suggesting a decrease in left ventricular hypertrophy. In the 14 patients whose E.C.G. records suggested right ventricular hypertrophy, the post-operative findings were as follows. In the nine patients with recognized pulmonary hypertension the E.C.G. was not available in one case owing to post-operative death; in three, the evidence of right ventricular hypertrophy disappeared, and in the remaining five it persisted. Of the five patients not thought to have had pulmonary hypertension no post-operative record was available in one, and V_1 became normal after operation in only one. In the additional case without pulmonary hypertension, in which R_{V1} was 10 mm. and S_{V6} 14 mm., the E.C.G. showed no change following operation.

Discussion

Aetiology. The physical phenomenon of spontaneous closure of the ductus arteriosus is not understood. The fundamental cause of persistent patency of the ductus is therefore also unknown. In this series there is the usual marked predominance of females, which may suggest an endocrine factor. There is only one instance of maternal rubella during pregnancy, a lower incidence than in some other series (Stuckey, 1955), and there is no record of neonatal asphyxia, which has recently been incriminated (Record and McKeown, 1953, 1955). Information concerning this was, however, only obtained from the mother and it is not unlikely that the neonatal hospital records of these children might reveal a different picture as the mothers would not necessarily have known that asphyxia had occurred.

Incidence. The condition is not uncommon and formed 16% of the first 1,200 cases referred for suspected heart disease.

Clinical Diagnosis. Although the patent ductus probably gave rise to symptoms in about one-third

of cases, the majority of children were referred to the heart clinic on account of the cardiac murmur.

PHYSICAL SIGNS. A classical Gibson murmur characteristic of patent ductus arteriosus, usually with a thrill, was present in 90% of our cases. In these patients the diagnosis was considered to be established by this physical sign alone and further examination, electrocardiography and radiology were completed mainly to exclude associated cardiac abnormalities and to elicit evidence of pulmonary hypertension which might require investigation by cardiac catheterization. In a few of these cases the murmur varied considerably from time to time, especially in respect of its loudness during diastole. This phenomenon is well recognized in patent ductus arteriosus and may be partly due to variation in the position of the heart affecting the relations between the ductus and great vessels and therefore the volume of the shunt. In one case at operation it was found that the characteristic thrill over the pulmonary artery was only present when the apex of the heart was lifted by the surgeon's hand and the long, narrow ductus, which lay very obliquely between the aorta and pulmonary artery, became more transverse and, probably, more patent. Under normal circumstances the degree of distension of the stomach and posture of the child might act in a similar manner. The murmur was less typical, in that it did not extend throughout diastole, in seven cases all with pulmonary hypertension, but the crescendo in late systole running up to an accentuated second sound and immediately followed by a softer fading diastolic murmur was very suggestive of a patent ductus. In this type of murmur and in still less typical murmurs, phonocardiography may be helpful in revealing their characteristics, but it was not used to any extent in this series. The murmur and thrill of an aorto-pulmonary fistula may be similar to that of a patent ductus and it is of interest that we have not seen an example of this condition in this series, whereas in some published series additional patients with such fistulae have been reported.

An exceptionally loud second sound in the pulmonary area indicated pulmonary hypertension in seven patients, in some of whom the sound was only just split or single, due probably to synchronous closure of aortic and pulmonary valves. In many of the other cases, as has already been stated, we found it difficult to decide whether a loud second sound was within the limits of normal or not. A soft pulmonary sound would, of course, throw doubt on the presence of a patent ductus or suggest an associated pulmonary stenosis.

A mid-diastolic murmur was heard in the mitral area in a high proportion of cases once its frequency had been appreciated, and it is of interest that its incidence bore a closer relationship to radiological evidence of increased size of the heart and left ventricle, to hilar enlargement and to pulmonary hyperaemia than any other physical sign. It is ascribed to the increased flow through the mitral valve which results from augmentation of the pulmonary blood flow by the volume shunted through the ductus, and will be most easily heard when the flow is large. Occasionally it is accompanied by a diastolic thrill.

A definitely collapsing pulse and wide pulse pressure suggested, on the whole, a large rather than a small patent ductus, while in many of the children a normal blood pressure and pulse were found in the presence of a normal or medium-sized ductus. A normal pulse and/or pulse pressure were, however, also found in six of the 11 cases with a large ductus complicated by pulmonary hypertension.

Radiography. The radiological findings in these children were similar to those in other published series. They were, on the whole, more marked when the ductus was large and the changes following operation were also more striking after the closure of a large ductus. In some cases reversion towards normal appearances was progressive for 18 months or longer, but details of these later films are not included in this paper. As might be expected, there was less change in those cases in which closure of the ductus was known to be incomplete or recanalization had occurred.

Electrocardiography. The electrocardiographic evidence of left ventricular dominance which was found in over a third of our patients throws light on the nature of the cardiac enlargement which occurs with persistent patency of the ductus arteriosus. The characteristics of 'diastolic overload' of the left ventricle, suggesting simple dilatation of that chamber without hypertrophy (Sodi-Pallares and Marsico, 1955; Landtman, 1954), were found in 33 cases, while evidence of 'systolic overload' was only seen in two. The latter type of record is found with muscular hypertrophy of the left ventricle which, in cases of patent ductus arteriosus, is said to be due usually to associated systemic hypertension, but in these two the blood pressure was normal, being 110/75 and 105/85 mm. Hg respectively. However, the E.C.G. in both cases reverted to normal soon after operation and it seems unlikely that the ventricular muscle could lose its hypertrophy so rapidly. Mannheimer (1948) demonstrated that a large number of patients with

patent ductus arteriosus showed electrocardiographical evidence of coronary insufficiency after exercise and it is possible that inadequate diastolic filling of the coronary arteries causes the inversion of the T wave and depression found in these cases. In this event, rapid reversion of the E.C.G. to normal would be expected after surgical closure of the ductus.

Conclusive evidence of right ventricular hypertrophy in a case of patent ductus arteriosus is of considerable importance. Electrocardiography suggested this change in 14 of the 83 cases fully examined, if one accepts 10 mm. as the upper limit of normal for R_{V1} (Switzer and Besoain, 1950). The lack of evidence of pulmonary hypertension in some of these children and its occurrence in some of those with a normal E.C.G., however, illustrates the need for caution in interpreting right ventricular dominance in these cases, especially in young children, in whom a variable degree of this pattern is normally found; and it is possible that in lead V_1 an R wave of 13 to 15 mm. or even more may on occasion be unassociated with right ventricular hypertrophy and therefore within the limits of normal. However, a study of our more recent cases suggests that greater attention should in future be paid to lead V_{3R} which appears to give more consistent evidence of right ventricular change than lead V_1. This is in line with the recent observation that V_{4R} in adults gives the most reliable information concerning the right ventricle (Camerini, Goodwin and Zoob, 1956).

Cardiac Catheterization. As stated above, this method of investigation was employed in a few cases in this series only. In future it should be necessary even less frequently, as the condition will probably be diagnosed in the majority of children at the latest on school entry at the age of 5 years when it will only occasionally be complicated by significant pulmonary hypertension. In some cases, however, it will still be necessary in order to establish the diagnosis and the direction of the shunt when this is in doubt.

In view of the technical difficulties that may be encountered in closing a large ductus, it is helpful to the surgeon if the size of the vessel can be predicted before operation. The data from this series which might have been useful in achieving this aim are set out in Table 6, which compares the findings in large and small ductuses, omitting those of intermediate size.

It will be seen that there is a rough correlation between the clinical findings and the external diameter of the ductus. That the correlation is not closer is not surprising, as one would expect that the clinical findings would depend more on the blood flow through the ductus than upon its external diameter and it has shown that there is no direct relationship between these two (Fowler and Mannix, 1955; Taylor, Pollack, Burchell, Clagett and Wood, 1954). Two variable factors which may account for this are the thickness of the wall of the ductus and the angle at which it joins the pulmonary artery. While, therefore, it is impossible from clinical findings alone to predict accurately the size of a ductus, one may with a fair degree of certainty suspect the presence of the unusually large vessel which frequently gives rise to difficulties at operation. Pulmonary hypertension may also give rise to difficulty at operation and should be diagnosed beforehand. Its presence will be suspected when the pulmonary second sound is loud and closely split or single and when there are physical signs, E.C.G. changes and radiological appearances of right ventricular hypertrophy. In addition, the peripheral pulmonary plethora may be reduced by arteriolar constriction so that the outer parts of the lung fields appear light while the hila remain engorged. In all such cases the pulmonary artery pressure must be measured and the direction of the shunt established by cardiac catheterization.

TABLE 6
RELATION OF FINDINGS TO SIZE OF THE PATENT DUCTUS

Findings	Patent Ductus up to 7 mm.	Patent Ductus over 10 mm.
Symptoms	25%	86%
Abbreviated murmur	Nil	43%
Diastolic B.P. under 50 mm. Hg	22%	61%
Diastolic murmur at apex beat	20%	82%
Hilar dance	14%	50%
E.C.G. $S_{V1}+R_{V6}$ over 35 mm.	32%	69%
Radiological C/T ratio over 56%	22%	72%

Treatment. Policy with regard to treatment must depend first upon our knowledge of the outcome to be expected in untreated cases. Shapiro and Keys (1943) expressed the situation clearly when they wrote that patent ductus arteriosus is a time bomb with a long fuse but still a bomb. They found that 80% of patients with patent ductus arteriosus eventually died from the effects of it and that the expectation of life was only 35 to 40 years. Campbell (1955) reviewed 20 patients still alive at 35 years or more. Nine were losing ground by the age of 42 at the latest and a further six showed marked E.C.G. and radiological evidence of cardiac enlargement. In addition to a shorter expectation of life, there is commonly a reduction of the cardiac reserve which leads eventually to congestive cardiac failure;

pulmonary hypertension develops in many cases and results in a reversal of the shunt through the ductus with *cyanose tardive* (Gross, 1952); and infective endocarditis may supervene. These complications are seldom seen in childhood but they present an unpleasant prospect for the untreated adult. During childhood growth may be limited (Porter, 1947; Muir and Brown, 1932), and was seen as a general phenomenon in this series, but the weights and heights recorded were not considered to be sufficiently accurate for detailed analysis.

While spontaneous closure of a patent ductus arteriosus has been reported, in exceptional cases as late as 34 years of age, its rarity does not justify the expectation that it will occur in any individual case (Brown, 1950; Campbell, 1955).

It is therefore desirable that every patent ductus diagnosed during childhood, in which the shunt is from left to right, should be closed surgically. This practice now has wide support, even when the aortic and pulmonary artery pressures are almost balanced (Bonham Carter, 1954). It is, however, essential that such operative treatment must be as nearly as possible devoid of risk if it is to be recommended universally as a prophylactic measure in children, many of whom are without symptoms. In this series no patient died following ligation of a patent ductus arteriosus. The single death was in the child with advanced pulmonary hypertension and reversal of shunt under the conditions of the operation, whose ductus was not ligated, in conformity with the view that ligation in such cases usually proves fatal. Twenty-three per cent. of our patients were under 4 years of age and 66% under 7 years when submitted to surgery. The procedure was tolerated well by the great majority, especially by the toddlers, many of whom seemed to be in normal health 48 hours after the operation. It has therefore become our practice in all straightforward and uncomplicated cases to advise closure of a patent ductus as soon as it is convenient.

The relief of symptoms, and the radiological and electrocardiographic evidence of decrease in the size of the heart in this series following operation indicate the possible reversibility, at any rate during childhood, of the cardiac changes caused by patency of the ductus, and support the policy of early closure. These findings are in agreement with those of Mannheimer (1948) who used an elaborate radiological technique for estimating the heart volume in 14 cases and found that ligation of a patent ductus arteriosus was followed by a decrease in volume in 12.

The good functional result indicated by this evidence was seen in the majority of cases. In an appreciable number of such patients, however, persistence or recurrence of a typical murmur suggested incomplete closure, or recanalization of the ductus. In this respect our experience of simple ligation of a ductus is similar to that of others (Sellors, 1948; Potts *et al.*, 1949; Gilchrist, 1948; Shapiro and Johnson, 1947), namely, that it will not always accomplish complete and permanent obliteration of the vessel. Although incomplete closure or recurrence are usually not accompanied by a shunt as large as before operation and are not, therefore, so liable to result in cardiac failure, nevertheless the possibility of infective endocarditis persists and a second attempt at closure is advisable, unless the surgeon considers the danger of further interference to be too great. It was for this reason that the more difficult operation of division of the ductus was adopted by Gross and others (Gross, 1952), even though the mortality rate of the procedure may be 2% or more in the best hands.

Summary

One hundred and eight children treated surgically for patent ductus arteriosus have been reviewed. The results of operation are analysed and the diagnosis of the condition is discussed.

We are grateful to Mr. F. Ronald Edwards and to Mr. B. J. Bickford for the surgical treatment of these patients and for the operative findings; to Dr. G. J. Rees for the anaesthetics; to Dr. Nora Walker and Dr. J. K. Walker for the radiological findings; to Dr. R. E. Rewell and his laboratory staff for the estimations of blood oxygen saturation; and to Mr. E. J. Caldwell and Mr. N. Clark for the electrocardiograms. We also wish to thank Professor Norman Capon for helpful criticism.

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HYDROCEPHALUS ASSOCIATED WITH OBLITERATION OF THE LONGITUDINAL SINUS

BY

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(RECEIVED FOR PUBLICATION APRIL 16, 1956)

There are theoretically three possible causes of hydrocephalus; first, an excessive production of cerebrospinal fluid, secondly a block in its circulation and thirdly a defect in reabsorption of the fluid. The majority of cases belong to the second group, that is obstruction to the circulation, and examples of hydrocephalus due to a defect in reabsorption from the subarachnoid space via the pia-arachnoid villi are extremely rare (Potter, 1952; Russell, 1949).

The purpose of this communication is to report two cases, one of a child dying at the age of 2 years in whom hydrocephalus was due apparently to complete organization of the longitudinal sinus over which a bony ridge had developed, and a second child with a history suggesting a cerebral sinus thrombosis, and in whom the development of a similar bony ridge suggested the same aetiology.

Case Reports

Case 1. This child was three weeks premature. Three weeks after birth he became ill with a temperature of 104° F. and was very sleepy and lethargic. He was given medicine by the family doctor, and appeared to recover from the acute illness, but he still remained for long periods of the day staring in front of him, and the mother thought his eyesight was very poor. At 6 months of age the mother thought his head was large and he was noticed to have a convergent squint. He did make a little progress in general development, but was far below the normal development for the age of 2 at which time he was admitted to hospital.

The head circumference was 24¾ in. and an anterior fontanelle was felt to the right of the midline. Further examination revealed another depression to the left of the midline. He was able to follow a light with his eyes, and would smile and move objects from one hand to the other, but did not say any words with meaning and was not able to drink from a cup.

General physical examination revealed nothing unusual apart from the hydrocephalus. There was no spina bifida.

Ventricular studies showed a symmetrical gross hydrocephalus. The ventricular pressure was more than 400 mm. and the pressure in the lumbar fluid was also more than 400 mm. Three millilitres of phenol red was introduced into the ventricular fluid and appeared in a short time in the lumbar fluid, and the hydrocephalus was thus shown to be communicating.

Following these investigations there was some infection of the cerebrospinal fluid with coagulase-negative *Staphylococcus albus*, which cleared up with antibiotics. After an unsuccessful attempt to drain the cerebrospinal fluid into the gall bladder an anastomosis was made between the lumbar theca and the left ureter after removal of the left kidney. This procedure was well tolerated and the child went home two weeks after operation, very well and with an obvious depression of the peculiar fontanelle on each side of the midline. The child died quite suddenly a week later.

NECROPSY. The body was that of a male child, with gross hydrocephalus, but no other external anatomical deformities.

The serous cavities and the abdominal viscera showed no notable abnormality. The appearance of the polythene catheter in the left ureter suggested that there had been some obstruction to the flow of cerebrospinal fluid. The surface of the brain was quite moist, and the convolutions were not abnormally flattened, as is usual in obstructive hydrocephalus. The cortex was approximately 4 mm. thick at the vertex, gradually becoming

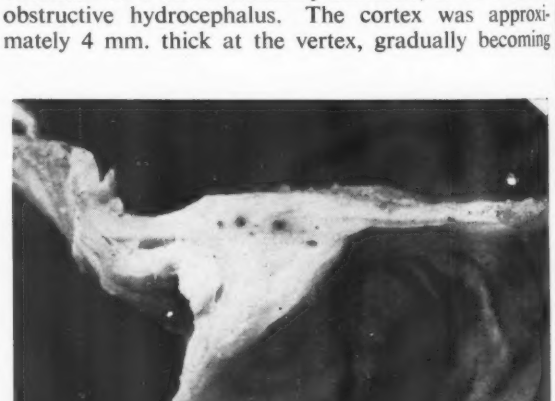

FIG. 1.—View of the falx, longitudinal sinus and attached dura showing the apparent complete obliteration of the sinus. (×1.)

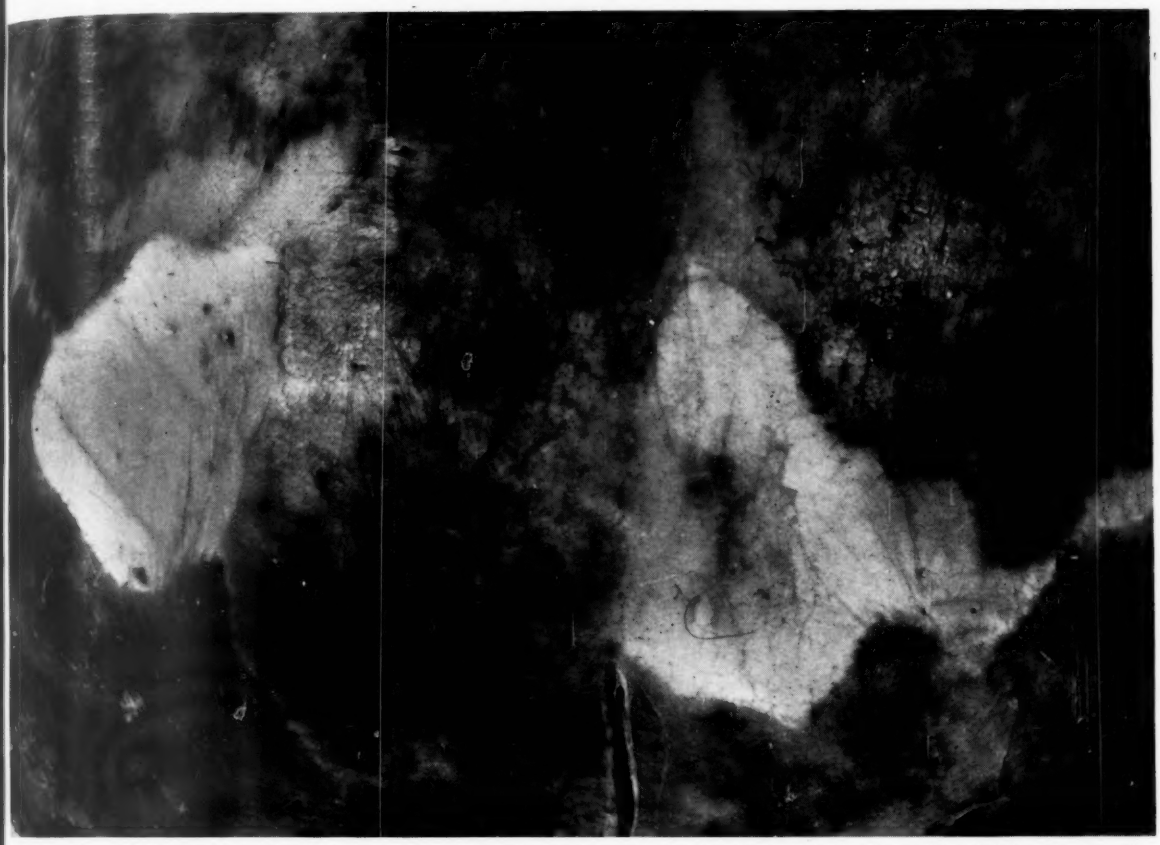

FIG. 2.—View of the outside of the skull at the site of the anterior fontanelle showing the longitudinal bony ridge dividing the normally diamond-shaped space. (×1½.)

thicker in the lateral direction and in the region of the occipital poles.

There was a fine granularity over the inner surface of both ventricles, but no brown staining or other evidence of haemorrhage.

The third ventricle was enlarged, and the choroid plexus throughout the lateral ventricles appeared normal. The aqueduct between the third and fourth ventricles was probably within normal limits.

The fourth ventricle appeared to be slightly enlarged. The cerebellum and medulla showed no Arnold Chiari deformity, and the spinal cord and column were normal. There was no meningocoele or spina bifida.

The longitudinal sinus appeared at first sight to be completely converted into a firm, fibrous mass (Fig. 1), but on closer inspection there were a few small blood vessels within this. The vessels leading into the longitudinal sinus were remarkably small, and there was no evidence of scar tissue or altered blood around them.

The organization of the longitudinal sinus ended abruptly at the tentorium where the sinus was joined by a fairly large blood vessel running in the falx. The straight sinus and lateral sinuses were normal. The skull showed a remarkable thickened, dark, bony ridge immediately over the longitudinal sinus throughout the whole length of the vault. This bony ridge completely divided the anterior fontanelle into two triangular lateral fontanelles (Figs. 2 and 4).

No notable abnormalities were found in the sections from all of the abdominal or thoracic viscera, with the exception of the lungs which had small, long-standing areas of collapse. The longitudinal sinus (Fig. 3) consisted of a dense mass of collagenous material containing several small, thin, strand-like channels of blood vessels lined by a single layer of endothelium. No altered blood pigment was found to suggest thrombosis with canalization. Sections taken from different parts of the longitudinal canal showed a similar picture.

The choroid plexuses appeared normal, and the irregularity of the lining of the ventricles was due to a general undulation of surface, and not to any local disease. No inflammatory changes were seen throughout the ependyma.

The child apparently died as the result of excessive salt loss due to unrestricted drainage of C.S.F. into the urinary tract; we have seen other children who have died in this way.

No gross developmental deformities were found in any of its systems, and the brain, the falx,

FIG. 3.—Low-power view of the central area of the longitudinal sinus showing dense connective tissue and a few small blood spaces. (Haematoxylin and eosion × 50.)

tentorium and foramen magnum suggested that there were no congenital deformities in the brain at the time of birth. The hydrocephalus was clinically of the communicating type, and no obstructive cause for hydrocephalus was found at necropsy; in fact the external appearance of the brain suggested that the brain had been subjected to pressure on both sides instead of the usual inner side only.

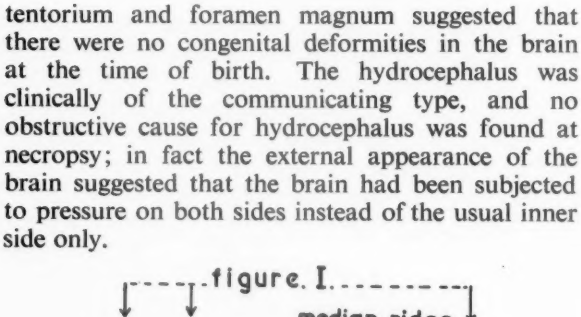

FIG. 4.—Diagram showing the bone ridge and location of the previous figures.

The longitudinal sinus was almost completely replaced by fibrous tissue of very long standing. While the cause of this fibrous replacement was not obvious, if there had been a gross neonatal longitudinal sinus thrombosis it is likely that all of the blood pigments would have been resorbed by this time. Attempts were made to cut sections of vessels from the meninges over the upper surface of the brain, but no pia-arachnoid villi were found.

We feel justified in suggesting that the hydrocephalus in this child was due to a removal of the absorptive mechanism over the cerebral hemispheres by way of the longitudinal sinus. Since the vascularity of the membrane overlying the longitudinal sinus is bound to be intimately related to the sinus, it is difficult to dissociate the overlying bony ridge in the child from the abnormal underlying sinus. It would seem most probable that this abnormal bone production was a direct result of the obliteration of the sinus. The entire clinical picture could well be due to thrombosis preceding the obliteration of the sinus.

Case 2. This baby was a first child, and, apart from toxaemia of pregnancy from about five months, the mother was quite well. The baby was born somewhat postmaturely by forceps delivery. At 1 week of age, he had meningitis due to *Bact. coli*. This responded well to streptomycin and chloramphenicol, and he appeared to make a complete recovery.

At 3 months of age it was noticed that his head was increasing rapidly in size and at that time was 17 in.

He was admitted to the Children's Hospital, Sheffield, in December, 1953, and was found to have a communicating hydrocephalus in which the ventricles were enormous. The head circumference was 20⅞ in. An anastomosis was made between the spinal theca and the left ureter after removal of the left kidney. Drainage of the cerebrospinal fluid appeared to be perfectly satisfactory, and the child was given an additional 3 g. of salt per day to compensate for the loss of electrolytes into the bladder. He was discharged home after 11 days, and appeared to be quite well.

He was again seen three and a half months after the operation. The shunt appeared to be working quite well. The anterior fontanelle was felt to be divided by a bony ridge into two lateral fontanelles. These fontanelles were depressed.

The last time the baby was seen at the Children's Hospital was nine months after operation, when he was 14 months of age and appeared to be making quite good progress. He was still not able to sit up because of the weight of the head, but had started to say words. The head circumference at that time was 23⅜ in.

The baby was admitted to another hospital 11 months after operation with a temperature of 103° F. due to an acute tonsillitis. There was no sign of meningism at that time, but he died within 24 hours.

The cerebrospinal fluid in the spinal theca was found to be infected, and the cause of death was given as meningitis superimposed upon hydrocephalus.

The pathologist who carried out the necropsy observed the abnormal bony ridge dividing the anterior fontanelle, but did not deliberately examine the cerebral sinuses, or attempt to determine a cause of the hydrocephalus.

The general condition of the child was satisfactory up to the time that he had a severe infection. Following this, hydrocephalus developed, and later the bony ridge overlying the longitudinal sinus in the skull was observed. The child had a communicating type of hydrocephalus which was apparently temporarily relieved by the theca-ureter shunt.

Discussion

The earliest description of hydrocephalus associated with obstruction of the central venous return known to us is by Browning (1887), who described a child aged 6 years who died with hydrocephalus following an illness lasting six months. In this child there was thrombosis of the straight sinus, and perisinusitis of the longitudinal sinus with apparent obliteration of the smaller vessels leading to the longitudinal sinus. Ellis (1937) recorded a child who developed hydrocephalus following a phase of semi-consciousness. He was able to demonstrate by means of a venogram that there was a complete obstruction to the posterior half of the longitudinal sinus. Bailey and Hass (1937) described two children, both of whom, after a period of normal growth, had convulsions, one at the age of 6 months and the other at 1 month. These children died, and at necropsy both showed long-standing thrombotic occlusion of the longitudinal sinus. Symonds (1937) and Russell (1949) refer to other suggestive, but not conclusive cases. Byers and Hass (1933) in a survey of 50 cases of intracranial venous thrombosis in children found hydrocephalus in eight of these. They state that the hydrocephalus had apparently preceded the thrombosis in five infants, but made no definite statements concerning the other three.

Discussion on the role of thrombosis in the production of hydrocephalus has largely centred around the conditions called 'otitic hydrocephalus'. Whereas some (Symonds, 1937) consider this condition to be a manifestation of cerebral sinus thrombosis, others (McAlpine, 1952) consider the condition to be due to an increased production of cerebrospinal fluid.

Thrombosis of the dural sinuses can produce bizarre features in adults. Ray and Dunbar (1951) describe four cases of 'pseudotumour cerebri', in which a block was demonstrated by venogram, and in one case they removed the clot in the posterior third of the longitudinal sinus, with apparent complete recovery of the patient. Martin (1941) and Martin and Sheehan (1941) reported a series of cases of cerebral sinus thrombosis occurring during the puerperium and causing increased intracranial pressure. Barr and Daws (1956) reported a tumour that apparently produced an increase in intracranial pressure due to obstructing the saggital sinus.

It has not been possible to produce hydrocephalus in experimental animals by occluding the cerebral sinuses. Bedford (1934) tied the great vein of Galen in the dog and found that there was rapid formation of collateral circulation, and Beck and Russell (1946) failed similarly with ligatures of the longitudinal sinus. However, the venous drainage in experimental animals is not identical with that in man, and the evidence obtained from animals is not conclusive. Surgical approach to the brain occasionally necessitates ligature of the longitudinal sinus. When the sinus is already partly occluded by tumour ligature apparently produces no ill effects (Dandy, 1940), but when no previous occlusion has taken place it seems that the sinus can only be ligatured with impunity anterior to the anastomotic Rolandic veins. If the whole vein is occluded, and the occlusion spreads to the cortical veins, extensive degeneration of the brain ensues (Jaeger, 1942). We have ourselves observed a very great variation in the anastomotic veins in infants' skulls. There are often large vessels running in the falx from the longitudinal sinus to the straight sinus, so that it is to be expected that the effects of occlusion of the longitudinal sinus are bound to vary much between individuals.

In our present Case 1, the whole of the length of the longitudinal sinus was occluded, but not the lateral sinuses or straight sinus. Anastomotic vessels were not seen, and the superficial vessels over the vertex of the brain appeared to be bloodless. No evidence of recent reaction was seen in the sinus nor evidence of old haemorrhage, and the sinus occlusion must have occurred in the distant past, possibly even *in utero*. In Case 2, we have considerably less evidence than in the other. There is a history of a cerebral incident with clinical meningitis during the newborn period. Cerebral venous thrombosis is frequent in such infants, and occlusion of the sinus could well have occurred at that time. We have never seen the longitudinal bony ridge over the anterior fontanelle in infants in whom hydrocephalus was due to inflammatory scarring around the base of the brain.

The presence of the longitudinal ridge dividing the anterior fontanelle (Fig. 2) was a striking feature of these cases, and we have not found any record of its occurrence with or without sinus occlusion. Since the venous blood from the dura and periosteal layers overlying the longitudinal sinus flow into the lateral sinus, it would seem justifiable to assume that the calcification is a direct result of the local diminution in the blood flow, due to the obstruction of the sinus.

Summary

Two children with hydrocephalus of the communicating type are described. In both, an abnormal bony ridge was present, covering the longitudinal sinus and dividing the anterior fontanelle into two parts. At necropsy, the longitudinal sinus in one case was almost completely occluded by dense connective tissue. It is suggested that the hydrocephalus in these children was due to a defect in resorption as a consequence of longitudinal sinus thrombosis, and that the bony ridge in the skull was also secondary to the sinus thrombosis.

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CONGENITAL FACTOR VII DEFICIENCY

A REVIEW WITH A REPORT OF A CASE IN AN INDIAN INFANT

BY

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(RECEIVED FOR PUBLICATION MARCH 5, 1956)

The presence of a factor, present in serum and capable of accelerating the conversion of prothrombin to thrombin, was postulated by Mann, Hurn and Magath (1947), Owen and Bollman (1948), and MacMillan (1948), as a result of experiments with plasma from patients treated with dicoumarol. Subsequently several groups of investigators have described factors with similar properties, and, as is customary in the field of blood coagulation, a like number of synonyms have appeared in the literature. Thus it seems likely that the co-thromboplastin of Mann, Barker and Hurn (1951), serum prothrombin conversion accelerator of de Vries, Alexander and Goldstein (1949), and of Alexander, de Vries, Goldstein and Landwehr (1949), convertin of Owren (1951a and b), prothrombin conversion factor of Jacox (1949), and factor VII of Koller, Loeliger and Duckert (1951), and the factor lacking in the chicks poisoned with dicoumarol of Dam and Søndergaard (1948), are all the same factor. Koller's (1954) term factor VII has gained considerable currency in the British and Continental literature and seems the most satisfactory term for our present state of knowledge.

Factor VII is found in normal serum; the demonstration of a plasma precursor has not yet been conclusively shown. It is stable on storage which immediately distinguishes it from factor V, the other prothrombin conversion accelerator, which is labile. It is readily absorbed by the same absorbants as prothrombin, i.e., $BaSO_4$, $Al(OH_3)$, $Ca_3(PO_4)_2$, asbestos, etc., and can be eluted from them by sodium citrate solution.

The role of factor VII in the coagulation process appears to be two-fold. First, Biggs, Douglas and MacFarlane (1953) showed it to be essential for the evolution of plasma thromboplastin, while Koller *et al.* (1951) and Owren (1951b) have demonstrated its role as a prothrombin conversion accelerator, and as a co-factor for tissue thromboplastin, being essential for the normal reaction of brain emulsion and prothrombin.

Factor VII deficiency may be either congenital or acquired. In the acquired category may be grouped deficiency resulting from therapeutic administration of the coumarin group of drugs, deficiency in hepatic disease, and in the newborn.

Cases of congenital deficiency of factor VII are rare; before 1950 they were reported in common with cases of factor V deficiency as hypoprothrombinaemias on account of the misconception then prevailing that the single-stage prothrombin time was a measure of plasma prothrombin.

A total of 14 cases designated as a deficiency of a serum factor, and probably corresponding to factor VII deficiency, have been found in the literature. Biggs and MacFarlane (1953) give some details of three probable cases of factor VII deficiency described before the factor itself was adequately characterized. These were the cases of Giordano (1943), Crockett, Shotton, Craddock and Leavell (1949) and Landwehr, Lang and Alexander (1950). Frick and Hagen in 1953 review a case previously described as a hypoprothrombinaemia by Hagen and Watson in 1948. This case was a 24-year-old woman whose defective single-stage 'prothrombin' time was wholly corrected by the addition of small amounts of serum. Alexander, Goldstein, Landwehr and Cook (1951) described the condition in a 4-year-old girl as 'an unrecognized coagulation defect rectified by serum and serum fractions' and showing that the missing factor was one readily absorbed by $BaSO_4$ from normal plasma or serum, but found that dicoumarol plasma, i.e., plasma from a patient under dicoumarol therapy, was efficacious to a considerable extent in correcting the defect and that its correcting power was little diminished by absorption with $BaSO_4$. These latter findings are difficult to reconcile with present concepts.

Owren in 1952 gave details of a similar case in a 38-year-old man, and Beaumont and Bernard (1953) described a case in a newborn baby. Lewis, Fresh and Ferguson (1953) describe two cases, one in a girl who died of haemorrhage at the age of 14 years, and one in a man of 32 years, and Jenkins (1954) a further case. Bell and Alton (1955) describe a case in a 29-year-old man in whom the condition was associated with Christmas disease, while de Vries, Kettenborg and van der Pol (1955) report three patients, in one of whom also Christmas disease and factor VII deficiency were found in association. These authors stress attaching significance to very small prolongations of the single-stage prothrombin time.

Clinical Details of Present Case

An Indian male child was admitted to the Paediatric Division of the Coronation Hospital on October 24, 1954, when he was 10 days old.

His mother stated that the infant had been bleeding from the mouth for six days and that she had noticed a change in the colour of the stools. He had also been vomiting after meals.

He had been delivered at full term at home by a midwife after an uneventful pregnancy. Labour was normal and lasted about six hours. The child appeared to be perfectly well at birth, and weighed 9 lb.

On the fourth day of life the mother first noticed bright red blood issuing from the child's mouth. He was seen by a general practitioner who gave him an injection of vitamin K. The next day he continued to bleed from the mouth and the mother also noticed that his stools now appeared black. The following day he vomited after his feeds and on one occasion the mother noticed bright red blood mixed with the vomitus. The bleeding persisted intermittently until the tenth day when he was admitted to hospital.

The mother was a healthy Indian woman aged 18 years and was born in Johannesburg. The father was aged 30 years and was born in India. The parents were first cousins. A previous sibling had died at the age of 4 days from 'haemorrhage'.

On admission the child appeared to be fairly well nourished weighing 8 lb. He did not appear to be unduly pale but he was slightly jaundiced. His hydration was good.

The head measured 14¾ in. in circumference. The anterior fontanelle was open and admitted four fingers. There was no craniotabes or separation of sutures. The eyes were normal although the conjunctivae were slightly icteric. The fundi were normal. Fresh blood was seen on the tongue which in its middle third appeared to have several small purplish spots. Similar lesions were seen at the junction of the soft and hard palate. The chest was normal in shape, moved freely on respiration, and the breath sounds were normal in character. The heart was not enlarged clinically and the heart sounds were normal. No masses were felt in the abdomen. The spleen was not palpable. The umbilical stump was still present; it was dry and the umbilicus appeared to be normal. No petechial haemorrhages were seen. The examination of the central nervous system did not reveal any abnormality. In view of the nature of the death of the previous sibling as well as the presence of haemorrhagic lesions on the tongue and palate in the patient a tentative diagnosis of hereditary telangiectasia was made.

The haemoglobin was 13 g. per 100 ml. The bleeding time was 4 minutes. The coagulation time was 6 minutes.

The umbilical stump separated and this was accompanied by haemorrhage from the umbilicus. The haemoglobin level dropped to 9 g. %. A blood transfusion of fresh blood was given. The patient had no further bleeding and was discharged on November 2, 1954.

On January 10, 1955, the patient was again brought to hospital with a history that he had been quite well until the day before admission when he again vomited his food which contained bright red blood. He appeared to be very sleepy and refused to take his feeds. On examination the baby was stuporose, the limbs flaccid and he was extremely pale. The anterior fontanelle was tense and bulging. He had no neck stiffness or head retraction. The eyes were deviated to the right. The mucous membranes of the mouth were pale and haemorrhagic purplish spots were again seen on the soft palate. The examination of the heart, chest and abdomen did not reveal any abnormality. He was generally hypotonic, and the reflexes were absent. A lumbar puncture was performed and the cerebrospinal fluid was blood stained. The patient had obviously had a cerebral haemorrhage.

In view of the persistence of the haemorrhagic tendency the blood clotting mechanism was investigated and the diagnosis of factor VII deficiency was established as described below.

After the establishment of the diagnosis an attempt was made to correct the deficiency by the administration of intravenous serum. Daily estimations of the thromboplastin time were performed but did not provide a satisfactory indicator of the efficacy of the treatment or of the amounts of serum required. Clinically, the bleeding appeared to be controlled by the administration of serum. On August 3, 1955, the patient died suddenly as a result of a fresh cerebral haemorrhage.

Post-mortem examination revealed a recent cerebral haemorrhage in addition to a large haemorrhagic cyst from a previous haemorrhage which occupied the whole of the left parietal lobe. Nothing of significance was found in the other organs.

Investigations

All the methods used are as described by Biggs and MacFarlane (1953). The bleeding time: (method of Ivy) was 1 minute. The clotting time (method of Lee and White) averaged 1 minute 45 seconds. Platelets numbered 400,000 per c.mm. (method of Kristensen, modified by Lempert), and appeared morphologically normal on stained smears.

Capillary resistance (tourniquet test) was normal. The thromboplastin time (single-stage 'prothrombin time') was performed on numerous occasions. It ranged from 3 minutes 55 seconds to 1 minute 5 seconds. Addition of 10% 'alumina plasma', i.e., normal plasma absorbed with aluminium hydroxide as described by Biggs and MacFarlane, did not result in any diminution of the thromboplastin time, but on the addition of 10% of normal serum, the time was reduced to normal (12 seconds).

The times recorded in a typical thromboplastin generation test are recorded in Table 1 and Fig. 1. A defect is clearly demonstrated in the patients' serum.

TABLE 1

THROMBOPLASTIN GENERATION TEST

Incubation Time (min.)	Patient's Alumina Plasma 1:5 Patient's Serum 1:0 Normal Platelets (sec.)	Patient's Alumina Plasma 1:5 Normal Serum 1:10 Normal Platelets (sec.)	Normal Alumina Plasma 1:5 Patient's Serum 1:10 Normal Platelets (sec.)
1	65	39	41·5
2	38	17·5	32·0
3	28	10·5	23·5
4	23	11·0	18·5
5	20	11·0	18·5
6	20	—	20·0

The test was performed as described by Biggs and MacFarlane (1953). 0·3 ml. amounts of each reagent were incubated together as the reaction mixture and 0·1 ml. transferred to 0·1 ml. normal citrated plasma. The clotting time of this substrate is given in seconds.

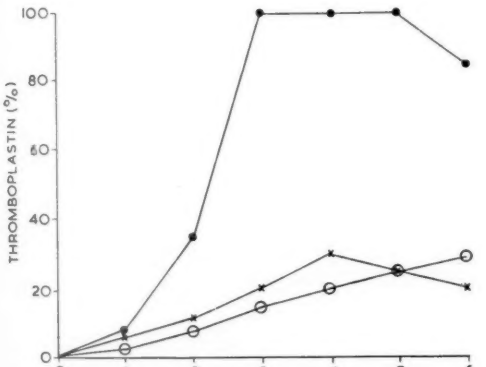

FIG. 1.—Results of thromboplastin generation tests The composition of the incubation mixtures is as follows:

0·3 ml. 1:10 dilution of normal serum.
0·3 ml. 1:5 dilution of patient's alumina plasma.
0·3 Suspension of patient's platelets.

0·3 ml. dilution of patient's serum.
0·3 ml. 1:5 dilution of patient's alumina plasma.
0·3 ml. Suspension of patient's platelets.

0·3 ml. 1:10 dilution of patient's serum.
0·3 ml. 1:5 dilution of normal alumina plasma.
0·3 ml. Suspension of normal platelets.

The possibility of a thromboplastin inhibitor being present was considered. To exclude the presence of such a factor, the recalcification time of various mixtures of the patient's and normal plasma was determined before and after incubation for two hours at 37° C. The results are shown in Table 2.

TABLE 2

TEST FOR THROMBOPLASTIN INHIBITOR

	Tube (ml.)				
Normal citrated plasma	1·0	0·9	0·5	0·1	Nil
Patient's citrated plasma	Nil	0·1	0·5	0·9	1·0
Recalcification Time (sec.) of these Mixtures					
Before Incubation ..	175	110	94	100	146
After incubation at 37° C. for 2 hours ..	270	240	230	220	392

The prothrombin content of the patient's plasma was determined by the two-stage method (Biggs and Douglas, 1953), with comparison of the areas. The curves of the patient and a normal are shown in Fig. 2, and the area of the normal is 17 sq. cm.; of the abnormal 21 sq. cm.

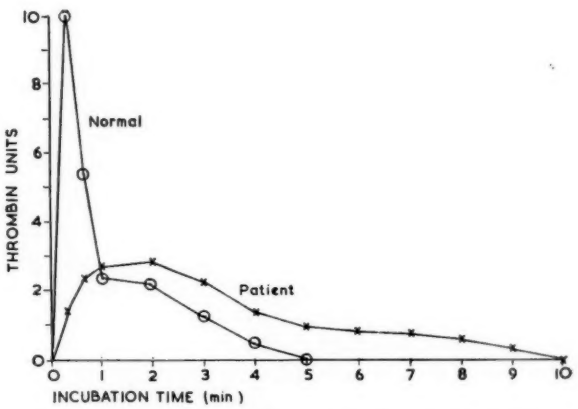

FIG. 2.—Prothrombin content tests performed according to the 2-stage method of Biggs and Douglas (1953).

The effect of the patient's serum on the thromboplastin time of a patient under treatment with 'tromexan', whose thromboplastin time was 40 seconds, was tested by the addition of 10% of the patient's serum; the time of the mixture was 46 seconds.

The addition of a small amount (0·1% final concentration) of a preparation of factor VII (Biggs and MacFarlane, 1953) to the patient's plasma used in the thromboplastin time test completely corrected the defect.

The prothrombin consumption test was carried out as described by Merskey (1950). The plasma time was 50 seconds and the serum time 8 minutes, giving a prothrombin consumption index of 11%. This test was repeated after the addition of 10% of normal serum which had been incubated at 37° C. for two hours and aged at + 4° C. for 48 hours to ensure prothrombin

conversion and destruction of thrombin. The plasma time was in this case 19·5 seconds and the serum time 5 minutes, giving an index of 6·6%.

It is clear from the foregoing data, summarized in Table 3, that the patient's deficiency was one of factor VII.

It was found that the patient's own serum (after incubation for three hours at 37° C.) was to some extent efficacious in correcting the defective thromboplastin time. This anomaly was also noted by Crockett *et al.* (1949), Jenkins (1954) and de Vries *et al.* (1955, case 2) in their cases.

The addition of a very small amount of thrombin (Parke-Davis 'topical thrombin') to the single-stage thromboplastin time resulted in complete correction. After absorption of the thrombin solution with $Al(OH_3)$ there was no correction, suggesting that commercial thrombin may be contaminated with factor VII, a possibility supported by the work of Frick and Hagen (1953).

Spontaneous activation of the patient's plasma on standing was noted; and the thromboplastin time was longest when performed without delay. After two to three hours the time fell to about 65 seconds, about which level it then remained stable for some time.

Tests were carried out on the mother, father, paternal grandmother and grandfather, but no abnormality was found in any of these.

Discussion

Congenital factor VII deficiency is a rare condition; 10 of the 15 published cases have occurred in males. It seems very probable from the published cases that it is familial. In the present case the presumption is strong, although no tests were performed on the elder brother, that he suffered from a similar deficiency. Whether the fact that the parents are first cousins is of import is not known; neither shows any evidence of a factor VII deficiency, and there is no clear history of haemorrhagic diathesis in the family. The similarity of the case presented here with that described by Landwehr *et al.* (1950) is very striking. Both cases are the second children of first cousin marriages, and in both cases the previous child died of haemorrhage shortly after birth.

On the clinical side, manifestations of the haemorrhagic state became apparent at birth or very soon after in the majority of the published cases. Of the sites of haemorrhage, gastro-intestinal bleeding is reported in eight of 15 cases, haemarthroses in seven, epistaxes in six, haematuria and menorrhagia twice each and cerebral haemorrhage once. The prognosis would not seem to be duly bad from the

TABLE 3

SUMMARY OF LABORATORY FINDINGS ON RASHID

Bleeding time: ..... Normal
Coagulation time: (Lee and White) ..... Normal
Hess's Test: ..... Normal
Platelets: ..... Normal quantitatively and morphologically
Brain thromboplastin time (Quick's one-stage prothrombin time): ..... Greatly prolonged, but corrected by addition of 10% normal serum
Factor V (Biggs and MacFarlane's method): ..... Normal
Factor VII: (Biggs and MacFarlane's method): ..... Greatly diminished
Prothrombin content (Biggs and Douglas's method): ..... Normal
Thromboplastin generation test showed the presence of a defect in the patient's serum factors.

ADDITIONAL TESTS

Patient's Plasma	Normal Serum 1/10	Normal Alumina 1/10	Thrombin Topical (0·5 u/ml.) *	Thrombin Topical Absorbed with $Al(OH_3)$	Serum from Patient Treated with Tromexan†	Factor VII Preparation 1/10	Patient's Serum 1/10	Brain Thromboplastin Time (sec.)
0·1								65–234
0·09	0·01							12– 18
0·09		0·01						185–206
0·05			0·05					12– 13
0·05				0·05				50– 57
0·09					0·01			36
0·09						0·01		14– 16
0·09							0·01	32– 37

In each case 0·01 ml. brain and 0·1 ml. $\frac{M}{40}$ $CaCl_2$ solution added and the clotting time recorded.

* Clotted patient's plasma without brain and Ca in 80–100 sec.
† Thromboplastin time of 'tromexan' plasma 40 sec.

published cases: nine out of 15 were apparently still alive at the time of reporting and had survived to adult life, three had died. The remaining three were alive, but still in childhood.

Treatment can only be by serum, plasma or blood transfusion, logically the first. Correction of the abnormal thromboplastin time is found, but it seems (Beaumont and Bernard, 1953) to be extremely shortlived, only a matter of hours. Similar treatment, intravenous or intramuscular injections of normal serum, in the present case produced no lasting alteration of the abnormal laboratory tests, but appeared to have a beneficial effect on the duration of haemorrhage clinically.

The injection of synthetic vitamin K and K_1 preparation has been uniformly unsuccessful in the reported cases, and was tried in this case without any benefit either clinically or as shown by laboratory tests.

Summary

A case of congenital factor VII deficiency in an Indian child is described, with laboratory findings. The literature of these cases is reviewed, and the clinical features, prognosis, treatment and laboratory findings discussed.

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HAEMOLYTIC DISEASE OF THE NEWBORN DUE TO ANTI-DUFFY (Fy^a)

BY

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(RECEIVED FOR PUBLICATION MARCH 20, 1956)

So far as we know haemolytic disease of the newborn due to anti-Duffy (Fy^a) has not been reported. Race and Sanger (1954) say that no well authenticated case had been reported up to the time of publication of their book, while no such case is listed in the Current List of Medical Literature from 1951 to date. The following one is therefore placed on record.

Case Report

Mrs. Vall is group O, Rh-negative, Duffy-negative; her husband, group O, Rh-negative, Duffy-positive. Mr. Vall is O; MsNs; P+; cdE.cde; kk; Fy(a+); Le(a−). Mrs. Vall is O; NsNs; P+; cde.cde; Kk; Fy(a−); Le(a−); Jk(a+). Baby is O; NsNs; P+; cde.cde; kk; Fy(a+); Le(a−). Mrs. Vall's pregnancy record is as follows:

(1) In 1949, normal. The mother was transfused immediately following this delivery, which was complicated, and two weeks later she received another blood transfusion. There was no clinically adverse reaction following either transfusion.

(2) In 1952, anencephalic foetus.

(3) In 1953, six months' gestation stillbirth.

(4) In 1955, the present baby, a girl, was born at term on December 19, weighing 5 lb. 6 oz. The baby's colour appeared normal at birth. Jaundice was first noticed when she was 12 hours old. About the same time she began to pass brownish-red blood by rectum and to vomit swallowed blood. The jaundice deepened, and at 38 hours she was admitted to the Children's Hospital, Winnipeg. Her general condition was good. There was marked jaundice and a congenital anomaly of the thoracic spine was apparent, but there were no other notable findings on physical examination. The haemoglobin was 16 g.; reticulocytes 13·2%; total nucleated red cells 1,188/c.mm.; serum bilirubin, direct acting 0·5 mg., total 13·7 mg. %. The infant's blood grouping was O, Rh-negative, Duffy-positive. The direct Coombs test was positive, the reaction, however, being weaker than that usually seen in Rh sensitization of any clinical degree.

Immediate replacement transfusion was deemed unnecessary. The blood passed per rectum was shown by the alkali denaturation test to be adult blood which the foetus had swallowed *in utero*.

The bilirubin level continued to rise, being 18·7 mg. at 52 hours and 21 mg. at 76 hours. At this point, fearing the possibility of kernikterus, a replacement transfusion was done, using blood that was Vall-negative, Fy(a−). The bilirubin was reduced thereby to 13·3 mg.; rose slowly to a peak of 22·8 mg. at 114 hours, then fell, reaching 10·8 mg. at 212 hours. The jaundice was gone by the fifteenth day and the baby was discharged, apparently well save for the congenital anomaly of the spine. Radiographs showed the latter to be a hemivertebral formation extending from C7 to T8.

The diagnosis of haemolytic disease seems certain: the jaundice beginning within 12 hours of birth and progressing, the steady and marked rise in serum bilirubin, the high reticulocyte and normoblast count, and the positive direct Coombs test of the baby's blood on both days 2 and 4. The mother's serum did not react by the standard saline, trypsin saline or albumin methods with any group O cells, or by the indirect Coombs or trypsin indirect Coombs methods with cells that were Fy(a−) but contained the following antigens absent from her cells: M, C, C^w, D, E, Jk^b. Her serum did react strongly by the standard indirect Coombs method and weakly by the trypsin indirect Coombs method with her husband's cells and with eight other Fy(a+) cells but not with seven Fy(a−) cells. The antibody is anti-Fy^a; the titre was 8.

The Canadian Red Cross Blood Transfusion Service provided 10 samples of group O, Rh-negative blood from which a suitable donor was selected by an indirect Coombs cross-match with the mother's serum and by Duffy typing. No anti-Fy^a could be demonstrated in the baby's serum by saline, albumin or the indirect Coombs test, nor were we able to elute an antibody from the baby's cells taken at the start of the replacement transfusion on the fourth day; the direct Coombs reaction, however, was still positive at that time.

The mother was most probably sensitized by one or other of the earlier transfusions but we have so far been

unable to trace the donors. The other, but less likely, explanation would be from isoimmunization consequent on the father being Duffy-positive.

Summary

The fourth child of a woman who had had two transfusions six years earlier developed haemolytic disease of the newborn. The father and baby were Duffy-positive [Fy(a+)], the mother, Duffy-negative [Fy(a−)]. The mother's serum contained anti-Duffy (anti-Fy^a) and no other demonstrable antibody. The baby was successfully treated by replacement transfusion with Duffy-negative [Fy(a−)] blood.

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THE INTELLIGENCE OF CHILDREN WITH CLEFT PALATE

BY

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(RECEIVED FOR PUBLICATION MARCH 28, 1956)

When a baby is born with a serious congenital anomaly, such as hare lip and cleft palate, the paediatrician should be in a position from factual knowledge to discuss with the parents the prognosis of that condition, including the outlook for mental development. One of us (R.S.I.) recently witnessed a father's rejection of a newborn baby with marked hare lip. He said that he could not possibly allow the child to be taken home, and that it would have to be adopted. Discussion gave him a better understanding of the problem and led to his changing his mind. In such a case the paediatrician must have a knowledge of the prognosis, with particular regard to facial appearance and mental development.

We have been unable, in a thorough search of the literature, to find factual evidence concerning the intelligence of children with cleft palate. The impression of one of us (R.S.I.) was that a high proportion of these children proved to be mentally defective. The only reference to the subject which we have been able to find was in the book *Inheritance of Harelip and Cleft Palate* by Fogh-Andersen (1943) based on a study of 703 cases. He stated:

'It is as likely as not that the frequency of associated defects of intellect exceeds the accident coincidence.'

Among 17,000 feeble-minded individuals examined by the University Institute of Human Genetics at Copenhagen, there were 59 cases of hare lip and cleft palate. The expected incidence would be 20, so that the frequency far exceeded the expected figure. Fogh-Andersen stated that he had no other facts about the problem.

The Present Study

One hundred and twelve names in alphabetical order were taken from the list of the plastic surgeon, Mr. W. Hynes. The only patients excluded were those who were under 4 years of age. Sixty were boys and 52 were girls. The ages varied from 4 to 16 years, with a mean age at the time of testing of 7¾ years. Fifty-four of these had a hare lip and cleft palate; 58 had a cleft palate alone. The patients came from a wide area, mostly from Yorkshire, Lincolnshire, Nottinghamshire and Derbyshire, and a few came from further afield. They were in no way selected in regard to social class, for very few cleft palate patients were treated privately, and the few who were, estimated at two in the last four years, were treated by the same surgeon. (One such case was included in the study. His I.Q. was 90.)

Having obtained the names, we wrote to the parents, explaining the purpose of the study, and offering to pay travelling expenses if they amounted to a shilling or more. The result was disappointing, largely on account of distance. In all 61 came for testing. Two had died. We then asked for the help of the appropriate medical officers of health and school medical officers, and they had a further 19 tested and sent school reports on a further 17. A total of 80, therefore, had a full intelligence test. We were unable to obtain any information about the remaining 13 (Table 1).

TABLE 1
CHILDREN WITH CLEFT PALATE WITH AND WITHOUT HARE LIP

Number of Cases Tested		No. of Cases with School Reports	Died	No Record	Total
At Institute of Education	By Local Authorities				
61	19	17	2	13	112
80 (71%)			15 (13%)		

The test used by the Institute of Education and by the local authorities was the Terman and Merrill test.

Results

The results reveal a range of scores comparable with that of the general population, the highest being

140, and the lowest below 50. There were, however, more scores below the average than above it, the mean I.Q. being 95·4, with a standard deviation of 19·5. This mean is significantly lower at the 5% level than an assumed population mean of 100. Kennedy-Fraser (1949) in a study of a truly representative sample of 1,215 11-year-old Scottish children found a mean I.Q. on the same test of 102·5 (σ 20·05). There are no available studies of English children for comparison with our series.

The distribution of scores is shown in Table 2. Two of the cases scoring I.Q.s of less than 50 were arbitrarily given a ratio of 45, though one at least of those was very considerably below this level. One had an I.Q. of 50. Forty-seven had an I.Q. of less than 100, and 33 an I.Q. of over 100.

TABLE 2
RANGE OF INTELLIGENCE QUOTIENTS OF 80 CHILDREN WITH CLEFT PALATE

I.Q. Range	Frequency
131–140	2
121–130	2
111–120	12
101–110	17
91–100	15
81–90	15
71–80	9
61–70	3
51–60	2
41–50	3
Total	80

Standard deviation (σ) = 19·5.

Interpretation

The anomaly of cleft palate alone is genetically distinct from that of cleft palate and hare lip, and we therefore analysed the results for the two groups separately. There was no significant difference in the intelligence of these groups.

In order to determine roughly whether any unknown bias had occurred in the patients who had the Terman and Merrill test, we have studied the information available on the remaining 17 cases.

In the reports of five of the 17 cases the children are referred to as being above average in ability. One is a grammar school boy who will be taking his General Certificate of Education this year; another is at a technical school having obtained an I.Q. of 106 on a Moray House test. Three others are in 'A' streams in junior schools.

A further five cases are said to be of average ability and there are intelligence test results in two of them. One scored 103 on the Valentine individual test and another had a mean score of 94 upon two Moray House tests.

There are seven cases in the 17 who are reported as very much below average ability. Of these one has actually been ascertained as being educationally subnormal though unfortunately no actual test results are available. Three are in special classes for backward children and the others are variously reported as being very backward though not sufficiently so to warrant transfer to a special school for educationally subnormal children. One of these children had a mean I.Q. of 86 in two Moray House tests.

Even when the fact that these reports by teachers are based largely upon the attainments of the children and not upon intelligence test results it would seem that had they all been tested their mean I.Q. would not have been higher than the figure of 95·4 found for the tested group and in fact it might easily have been rather lower.

Of the 13 cases about whom no estimate of ability could be obtained, the letters to three inviting cooperation were returned by the post office because they could not be traced, in one case the child had left school, one was too ill to come, one was not asked through a clerical oversight and one parent could not come because of the distance. It is not known whether the remaining six letters reached their addresses, though it is known that in two of these cases the children were being educated in private schools.

In this small group there seems nothing to indicate that any biased selection has taken place which would have resulted in the I.Q.s of the group actually tested being lower than those of the remainder. In further support of this contention it is usually found, as we have done in another enquiry of a similar kind in the same area, that selection works the other way. Cooperation is usually most likely among parents of higher ability who tend to have children of above average intelligence.

It is considered, therefore, that there is a tendency for hare lip and cleft palate to be associated with less than average intelligence. This does not, of course, prove that the two disabilities are genetically connected with intelligence in the usual sense. The disfigurement of hare lip and the speech handicap of hare lip and cleft palate will in the past have been a severe handicap in marriage and it seems likely that sufferers will have had to accept mates of inferior social status and appearance, both of which are known to be in small degree associated with less than average intelligence. Hence in each generation where the disability has revealed itself there will have been a tendency for this differential mating and a lowering of the average I.Q. of the offspring.

It will be interesting to repeat this survey in, say, 15 years to see whether the lessening of the handicap by modern surgical techniques will have caused the mean I.Q. of cleft palate and hare lip patients to

have moved nearer to the mean of the general population.

Summary and Conclusions

Information was sought on the intelligence quotient of children with cleft palate with or without hare lip.

Of the 112 children taken without bias from an alphabetical list, two had died, 80 had a Terman and Merrill test, school reports were obtained on a further 17 children, and we have no records concerning 13.

The average I.Q. of those tested was less than the average figure for the population as a whole, averaging 95·4. Forty-seven had an I.Q. of less than 100; 33 had an I.Q. of over 100. The school reports of the additional 17 children gave the impression that the intelligence of those children was very similar to that of the tested ones.

We wish to thank the Board of Governors, the United Sheffield Hospitals, for defraying travelling costs of parents who brought their children for intelligence testing.

We also wish to thank Mr. W. Hynes, plastic surgeon, the United Sheffield Hospitals, for giving us access to his cases and records; to Miss Crowley, the Lady Almoner of the Children's Hospital, for helping to trace some of the patients; to Sister K. Booth, of the Children's Hospital, for supplying the names and notes; and to the following medical officers and others who so kindly cooperated in obtaining and supplying information about the children who failed to come up for the special examination and testing: Drs. W. T. G. Boul, W. S. H. Campbell, C. D. Cormac, D. J. Cusiter, B. R. A. Demaine, G. Higgins, C. W. W. Jeremiah, Mr. J. L. Longland, Drs. E. K. Macdonald, J. Maclachlan, L. F. McWilliams, J. E. Masterson, J. B. S. Morgan, G. A. W. Neill, G. Randall, R. G. Sprenger, J. A. Stirling, M. C. Taylor and J. M. Watt.

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A PATHOLOGICAL STUDY OF FIVE CASES OF PYELONEPHRITIS IN THE NEWBORN

BY

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(RECEIVED FOR PUBLICATION MARCH 27, 1956)

It is increasingly recognized that many problems concerning the aetiology, recognition and natural history of urinary tract infections are still unresolved, and this is particularly true of such infections in infancy. There is, for example, no general agreement about their incidence in the first months of life: Stansfeld (1954) has pointed out that pyelonephritis occurs more frequently in the first year than at any other age, and most frequently of all in the first month, but this distribution pattern has not been universally recognized. The divergence of opinion may derive from a failure to consider pyelonephritis as a possible cause of such symptoms as vomiting, anorexia, constipation, diarrhoea and poor weight gain, or from uncertainty in assessing the significance of those minor abnormalities in the urine which may be the only diagnostic feature of chronic pyelonephritis. The situation is further confused by disagreement over the interpretation of various lesions which may be found in the kidneys of small infants dying of renal disease so that even necropsy may not resolve clinical uncertainty.

Among the few existing reports of the morbid anatomical findings in cases of neonatal pyelonephritis are those of Chown (1927) who could find only nine cases in the earlier literature. To these he added detailed reports of 30 cases of 'pyelitis' in infancy. Most of his cases showed the changes of acute suppurative pyelonephritis but four with chronic pyuria showed in addition 'inflammatory lesions in various stages of healing'. Craig (1935) gave the post-mortem findings in six cases of acute pyelonephritis and Hunt (1936) described one case with unilateral acute suppurative pyelonephritis fatal 13 days after birth. More recently Claireaux and Pearson (1955) have recorded chronic pyelonephritis in a newborn infant.

The histological picture of acute pyelonephritis in early infancy is indistinguishable from that found at any other age; in the chronic stage, however, differences may appear which have hitherto been insufficiently recognized and it is the purpose of this paper to discuss them.

Material

Five cases of pyelonephritis in infants under 1 month of age are described. All of these were males and this is in keeping with the general tendency of neonatal pyelonephritis to be more frequent in boys. Four of the infants were born in the same hospital within a few months of each other. (Two other cases occurring in the same period have apparently recovered.) The fifth case was a brother of one of the other four. One infant died during the acute phase of his illness, two died later in uraemia and two succumbed to intercurrent infection.

Case 1. R.E., a male negro infant, was the second of twins born on March 25, 1954, after a normal pregnancy. He was a breech presentation, but was turned and extracted without difficulty. It is not known whether the twins were identical or fraternal. He progressed normally until April 12 when he was noticed to be jaundiced. Haemoglobin was 8·3 g. % and total serum bilirubin 7·4 mg. %; the direct Coombs test was negative and no sickling was demonstrable. On April 16 he became lethargic, anorexic and febrile, and was given terramycin. The white blood count was 35,000/c.mm. and blood culture yielded a growth of *E. coli* : the urine contained pus and also yielded *E. coli*. The organisms obtained from the blood and urine appeared identical except that the former was sensitive and the latter resistant to terramycin. In spite of vigorous treatment with penicillin and streptomycin he died on April 18, aged 3½ weeks.

GENERAL NECROPSY FINDINGS. The tissues were dehydrated and bile-stained.

The myocardium was pale and flabby and the ductus arteriosus and foramen ovale were widely patent. The lungs showed a few areas of collapse at the right base.

The stomach and small gut were distended and

contained white curdy material. The liver was deeply jaundiced, firm and without obvious pattern. There was a congenital stenosis of the common bile duct.

The left kidney (weight 25 g.) was considerably larger than the right (weight 17·5 g.) and showed extensive acute pyelonephritis. Inflammation was much less marked in the right kidney. No other abnormality was seen in the genito-urinary tract.

On section of the brain a large haemorrhage was seen in the region of the right caudate nucleus which communicated with blood in the ventricles.

MICROSCOPY OF THE KIDNEYS. The renal capsule was normal. Scattered throughout both the cortex and medulla were multiple abscesses in which bacteria could be demonstrated. In these areas some of the glomeruli had been destroyed; others were extensively infiltrated by polymorphs or showed periglomerulitis with fibrin. Many of the tubules were dilated and contained pus. Polymorphs and some lymphocytes had infiltrated the interstitial connective tissue. The blood vessels were normal. The renal pelvis showed acute inflammation with areas of necrosis and loss of lining epithelium.

Microdissection showed a number of the nephrons to be of premature type in that they were shorter than normal and lacked convolutions.

Case 2. C.T. was a male infant born at term on March 4, 1950, by spontaneous, normal delivery. He had a weak cry with stridorous breathing, and laryngoscopy was thought to show a fine web across the vocal cords. Progress was slow with increasing reluctance to feed; on May 18 he was febrile and the urine contained pus and was found to be infected with *E. coli* and *Str. faecalis*. The infection did not clear in spite of treatment and he became increasingly acidotic and azotaemic. He died on July 20, 1950, aged 20 weeks.

GENERAL NECROPSY FINDINGS. The body was slightly wasted with pale skin but no oedema. No congenital abnormality was found on external examination.

The heart weighed 40 g. and showed left ventricular hypertrophy. In the larynx, situated immediately above the vocal cords which did not seem to be well developed, there was a very thin, triangular, transparent membrane. All lobes of both lungs showed moderate congestion and oedema and patchy areas of collapse. The intestines, liver, pancreas, spleen, pituitary, thyroid and adrenals were normal.

Each kidney weighed 20 g. and the capsules stripped easily leaving a smooth pale surface. On section pallor was pronounced, the cortico-medullary junctions blurred and the pelves injected. The renal vessels and the remainder of the urogenital system were normal.

The brain and bones were normal.

MICROSCOPY OF KIDNEYS. The capsule of the kidneys showed no change. The glomeruli were reduced to about three-quarters of their normal number. Of those surviving, most were normal but some showed marked pericapsular fibrosis. A few showed capsular crescent formation; the majority of the crescents had undergone fibrosis (Fig. 1) but some remained cellular. Adhesions between glomerular tuft and capsule were also to be seen

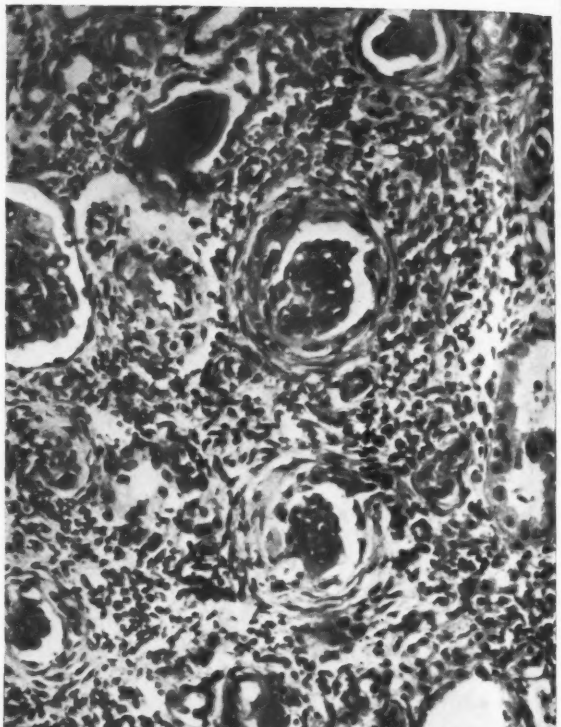

FIG. 1.—Case 2. Two glomeruli showing capsular crescents which have become fibrous. Note the dense interstitial infiltration with chronic inflammatory cells. (Haematoxylin and eosin ×150).

in a few. Occasional glomeruli were partly hyalinized, others had been converted into hyaline spheres. The damaged glomeruli tended to be grouped together into rough cortical wedges. There were no striking changes in the glomerular capillary basement membranes. 'Alterative' glomerulitis was seen in some glomeruli in unscarred areas.

In the areas of glomerular damage groups of proximal tubules were dilated and lined by flattened atrophic epithelium and contained pink 'colloid' casts. Occasional tubules were cystic. Some collecting tubules showed similar changes.

The interstitial tissue, particularly in the cortical wedges of glomerular and tubular damage, was heavily infiltrated by lymphocytes and plasma cells with very occasional polymorphonuclear leucocytes. There was also some fibrosis.

The arcuate and interlobular arteries showed mild productive endarteritis and the arterioles mild hyperplastic arteriolosclerosis.

The pelvis of the kidney appeared normal.

Nephron dissection (Fig. 2) showed that the proximal tubule was considerably shorter than normal and almost completely devoid of convolutions; in addition the epithelium was flattened and the lumen grossly dilated (Darmady and Stranack, 1955).

FIG. 2. Case 2. Microdissected nephron showing a short, straight grossly dilated proximal tubule with no convolutions and lined by flattened epithelium. (Phase contrast ×220.)

Case 3. A.T., a brother of Case 2, was born at term on June 26, 1954, by spontaneous normal delivery. He had a stridorous cry which led his mother to recall his brother's history, and on July 1 his urine was therefore examined. It contained scanty pus cells, a moderate number of red blood cells and gave a heavy growth of *E. coli*. On July 7 the blood urea was 40 mg. %. In spite of intensive antibiotic treatment urine cultures continued to yield various organisms including *E. coli*, enterococci and *Staph. aureus*. The urine also repeatedly contained pus cells, red blood cells and hyaline casts, albumin in considerable amounts, and reducing substances. On July 13 the blood urea level was 132 mg. % and remained high until death. On September 9 his systolic blood pressure was 150 mm. He became increasingly acidotic, developed heart failure, and died on November 5, 1954, aged 19 weeks.

GENERAL NECROPSY FINDINGS. The body showed oedema of the legs, scrotum, sacral region and eyelids. The abdomen was distended and the buttocks excoriated. The heart weighed 50 g. and showed great hypertrophy of the left ventricle, the wall being 1 cm. in thickness. Each pleural cavity contained about 10 ml. of clear yellow fluid. The lungs were oedematous and showed patchy, blue, sunken areas of collapse. The larynx and trachea were normal. There was a small peritoneal effusion of clear yellow fluid. The liver was congested and enlarged, weighing 237 g. The intestines, pancreas, spleen, pituitary, thyroid and adrenals were normal.

Each kidney weighed 20 g. and the capsules stripped easily, leaving a smooth pale surface showing foetal lobation. The cortico-medullary junction was blurred. The pelvis was normal. The remainder of the genito-urinary tract was normal.

The brain was oedematous. Bones were normal.

MICROSCOPY OF KIDNEYS. The kidney capsule showed little change. The glomeruli were reduced to about half their normal number. Of the remainder few were completely normal and there was a tendency for the damaged glomeruli to be huddled together. Some showed marked concentric pericapsular fibrosis; in these the tuft was often relatively normal, but on other occasions tuft and capsule had fused to form a hyaline mass. In some there was proliferation of the cells of Bowman's capsule with crescent formation (Fig. 3). A few mitoses were visible in these cell masses and occasional capsular spaces had been obliterated. In a few cases the crescents had undergone fibrosis. Adhesions between tuft and capsule were frequent. Examples of pseudo-crescent formation (Claireaux and Pearson, 1955) and partly hyaline tufts were also seen. The capillary basement membranes of some of the affected glomerular tufts were thickened in a patchy manner and occasional tufts contained small droplets of fat apparently deposited between the capillary loops. In a few instances the capsular space contained acidophilic material but there were no polymorphs.

Most of the proximal tubules were dilated and contained eosinophilic, P.A.S.-positive colloid casts. The lining epithelium was flattened, with no brush border,

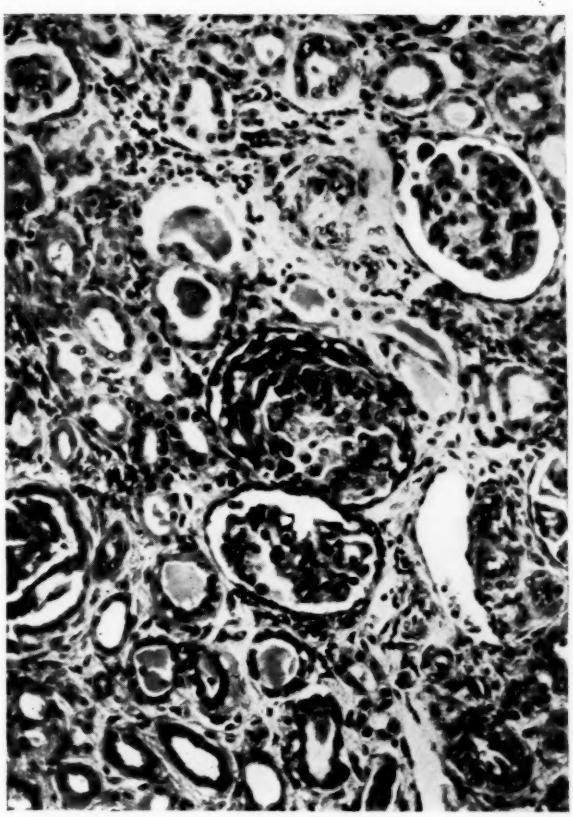

FIG. 3. Crescent composed of proliferating capsular epithelial cells. (Haematoxylin and eosin ×150.)

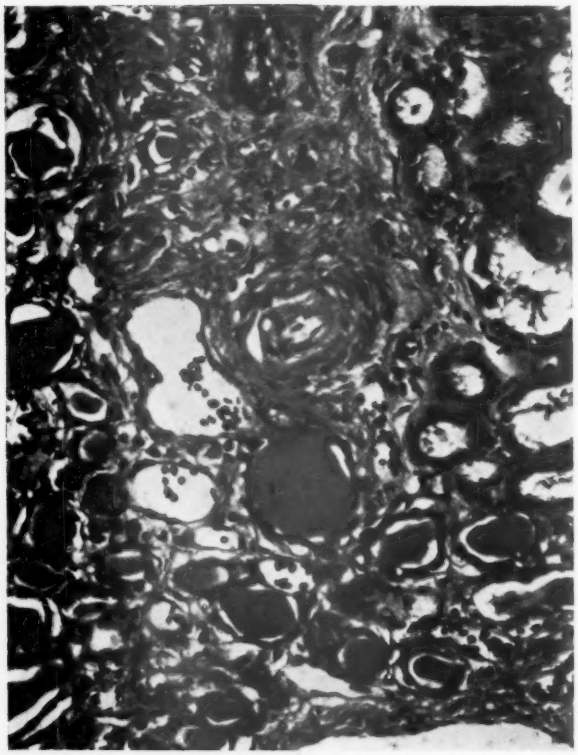

FIG. 4. Case 3. Numerous dilated tubules lined by flattened epithelium and containing 'colloid' casts. The artery shows productive endarteritis. (Haematoxylin and eosin × 160).

and lacked alkaline phosphatase. Many of the loops, distal tubules and collecting tubules contained pink casts, some of which were calcified. A few contained pus.

Large areas of interstitial tissue, particularly in the cortex, were densely infiltrated by plasma cells, lymphocytes, occasional eosinophils and histiocytes. In the medulla the chronic inflammatory infiltrate was much lighter. Interstitial fibrosis was also marked.

The arcuate and interlobular arteries showed marked productive endarteritis (Fig. 4) whilst many arterioles showed hyperplastic arteriolosclerosis and occasional fatty-hyaline change.

The epithelium of the renal pelvis was normal.

Nephron dissection showed the tubules to be essentially the same as those in the patient's brother (Case 2).

No organisms, inclusion bodies, cystine crystals or extramedullary haemopoiesis were found in this kidney.

Hyperplastic arteriolosclerosis was also found in the arterioles of the gut wall.

Case 4. S.R. was a boy born at term on August 25, 1954, by spontaneous normal delivery. On September 5 he began vomiting and on September 9 the urine contained many pus cells and yielded a mixed growth of micrococci and proteus. On the same day blood culture yielded a growth of *E. coli* and four days later an apparently identical coliform organism was cultured from the urine. On September 15 the blood urea level was 100 mg. % and the systolic blood pressure was 80 mm. He was given a prolonged course of sulphonamide and chloramphenicol, during which his general condition improved and his urine became free of pus cells but continued to yield a scanty mixed growth of enterococci, micrococci, proteus and coliforms. Blood urea fell to about 50 mg. % but did not return to normal. Treatment was stopped on September 28. He remained clinically well, but on October 21 the urine again contained pus cells and grew *E. coli* and *Proteus*, and the haemoglobin was 8·9 g. %. From October 25 to November 11 he was given sulphonamide, penicillin and streptomycin, in spite of which the urine continued to show a small excess of pus cells and a mixed growth of organisms. The blood urea level remained at 50 to 60 mg. %. His general progress was satisfactory until January 12, 1955, when he developed a slight cough: on January 15 his mother found him dead in his cot. At death he was aged 21 weeks.

GENERAL NECROPSY FINDINGS. The body was well nourished, showing cyanosis of the lips and finger nails and bile-stained fluid coming from the mouth.

The heart weighed 39 g. and showed left ventricular hypertrophy, moderate dilatation of the right side, and a few petechiae beneath the epicardium. There was frothy mucopus in the trachea, main bronchi and many of the smaller bronchi, particularly in the left lower lobe, with considerable injection of the lining mucosa. The lungs showed extensive, patchy, lobular collapse, most marked in the lower lobes, and generalized oedema. Microscopically there was a purulent bronchiolitis. The hilar lymph nodes were enlarged and haemorrhagic. The liver was enlarged and congested. The gastro-intestinal tract, pancreas, spleen, adrenals, thyroid, thymus and pituitary were normal.

The kidneys (weight 31 g. and 27 g.) were congested. The capsules stripped readily, exposing surfaces with a fine irregular granularity. No abnormality was seen on section. The pelves, renal vessels and the remainder of the urogenital system were normal.

The brain and bones were normal.

MICROSCOPY OF THE KIDNEYS. The renal capsule was normal. The glomeruli were slightly reduced in number. Most of the surviving glomeruli were normal, but in a roughly wedge-shaped area; they were closer together than usual and showed various changes, the commonest of which was marked concentric pericapsular fibrosis, often with relatively normal tufts. However, in some this had led to complete obliteration of the tufts so that only a hyaline sphere remained. Some showed adhesions between tuft and capsule. Occasional crescents were seen (Fig. 5) and a few primitive glomeruli.

In the patches where the glomeruli were affected some of the proximal tubules appeared atrophic with flattened epithelium. However, colloid casts were few, and dilatation was not a feature. The distal parts of the tubules seemed normal. Some primitive tubules were also seen.

Fibrosis and chronic inflammatory infiltration of the interstitium with lymphocytes, plasma cells and occasional eosinophils were features of the scarred areas.

The arcuate and interlobular arteries showed slight

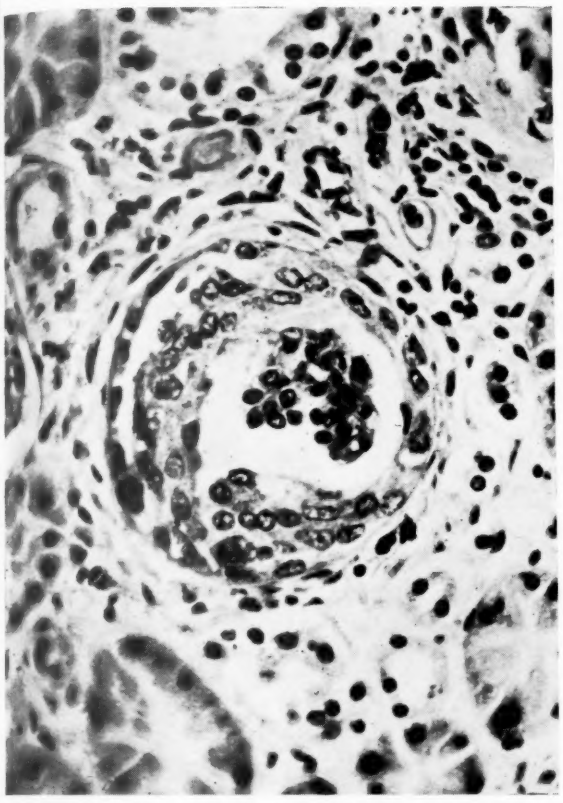

FIG. 5. Case 4. Glomerulus with a well defined cellular capsular crescent. (Haematoxylin and eosin ×350.)

productive endarteritis and the arterioles mild hyperplastic arteriolosclerosis.

The epithelium of the renal pelvis was normal.

Microdissection showed little evidence of persisting foetal nephrons. However, there were a number of long loops of Henle.

Arteries and arterioles in other organs were normal.

Case 5. R.F. was a male infant born at term on May 23, 1954, by spontaneous normal delivery. He made normal progress until June 5 when he refused his feeds and was noticed to be jaundiced. The liver was enlarged and the tip of the spleen and left kidney were palpable. On June 6 the urine contained pus cells and yielded a growth of *E. coli*. On June 9, the blood urea level was 160 mg. %. Between June 7 and July 6 he was treated with sulphonamide, penicillin, streptomycin, terramycin, chloramphenicol and erythromycin in various combinations. From mid-June the jaundice faded; whether it had been due to infection or to neonatal hepatitis was uncertain. His general condition improved slowly and irregularly and although the urine became free of pus cells it continued to yield a growth of proteus, coliforms and micrococci. By July 10 he was thought to be clinically well, and on July 28 he was discharged from hospital. He did not return for follow-up but was believed by his parents to be progressing satisfactorily until September 3 when he developed a severe attack of vomiting and diarrhoea. He was admitted to hospital but died on September 4, aged 14½ weeks.

GENERAL NECROPSY FINDINGS. The body was severely dehydrated. The heart weighed 40 g. and showed left ventricular hypertrophy. There was bilateral basal pulmonary congestion. The tongue was flabby and furred and there was hyperaemia of the mucous membranes of the stomach and small intestine suggestive of an acute gastro-enteritis. The liver and spleen were a little enlarged. The brain and bones were normal.

The kidneys (weight 27 g. and 24 g.) appeared normal and their capsules stripped easily exposing smooth subcapsular surfaces. No abnormalities were seen in the remainder of the urogenital system.

MICROSCOPY OF KIDNEYS. The renal capsule was normal. The glomeruli were reduced to about three-quarters of their normal number. Many showed pericapsular fibrosis with relatively normal tufts, some showed adhesions between tuft and capsule, others well marked capsular crescents. Some glomeruli had become completely hyalinized. There damaged glomeruli tended to be huddled together in rough cortical wedges. Unaffected glomeruli had undergone compensatory hypertrophy.

Many of the proximal tubules were dilated and some contained 'colloid' casts. Some of their lining epithelial cells were atrophic, others showed hyaline droplet degeneration. Distal and collecting tubules appeared normal. There were occasional casts in the collecting tubules, some showing calcification with tubular syncytial cell formation around them.

There was increased medullary interstitial and perivascular fibrous tissue, with occasional foci of calcification in cortex and medulla and a scattered infiltration by lymphocytes, plasma cells and occasional eosinophils and neutrophils.

The arcuate and interlobular arteries showed mild productive endarteritis, whilst the walls of occasional arterioles showed hyperplastic arteriolosclerosis.

The renal pelvis was lightly infiltrated by chronic inflammatory cells and subepithelial fibrosis was prominent.

These kidneys were not microdissected.

Arteries and arterioles in other organs were unaffected.

Discussion

Morphological Differences from Pyelonephritis in Adults. Case 1 died after an acute illness of relatively brief duration. The kidneys showed the typical histological picture of acute pyelonephritis, differing in no way from that seen in the older child or adult. In the remaining cases, there was a more prolonged illness, during which nitrogen retention and persistent pus cells and organisms in the urine led to the clinical diagnosis of chronic pyelonephritis. The histology of the kidneys in all four cases is believed to support this diagnosis, satisfying as it does the criteria laid down by Weiss

and Parker (1939), namely, (1) marked infiltration of the interstitial tissue with lymphocytes, plasma cells and eosinophils; (2) presence of pericapsular fibrosis; (3) presence of so-called colloid casts in tubules lined by atrophic epithelium.

The only other condition with which these histological changes might be confused is glomerulonephritis. In the present cases, however, many glomeruli were unaffected, whereas in glomerulonephritis it is usual for the changes to be diffuse with involvement of almost all glomeruli. Moreover, in those glomeruli in which pericapsular fibrosis was present, the tufts were often normal; in glomerulonephritis there is usually a fairly close correlation between the degree of fibrosis of the tufts and of Bowman's capsule. In glomerulonephritis the interval between glomeruli is diminished but these distances tend to be fairly uniform, in sharp contrast to the rather wedge-shaped clusters of glomeruli we have described. Lastly the interstitial infiltration with chronic inflammatory cells was greater in the present cases than is usual with glomerulonephritis.

However, the kidneys in these cases differed in two respects from those found in adults suffering from chronic pyelonephritis: (1) Macroscopically, there was little asymmetrical contraction or coarse, shallow scarring. (2) Microscopically, crescents in varying numbers were prominent.

Similar observations were made by Claireaux and Pearson (1955) in their case of chronic pyelonephritis in a newborn infant.

The absence of scarring may be a consequence of the comparatively short period of time for which the pyelonephritic process had been in progress, since all the cases were aged 21 weeks or under at the time of death. The presence of crescents does not necessarily exclude the diagnosis of chronic pyelonephritis. Crescents are not specific for glomerulonephritis, inasmuch as identical formations have long been known to occur in cases of malignant nephrosclerosis, subacute bacterial endocarditis, and sometimes in the chronic pyelonephritis of adults. In these latter conditions, however, the crescents usually involve only occasional glomeruli, not the majority as in glomerulonephritis.

It is possible that epithelial crescents develop in response to various stimuli more readily in the newborn period. Lowe, Henderson, Park and McGreal (1954) described crescent formation in a renal biopsy from a child of 1 year 9 months suffering from the severe form of idiopathic hypercalcaemia with low-grade secondary chronic pyelonephritis. Campbell and Henderson (1949), discussing asymmetrical cortical necrosis of kidneys in infancy, mentioned crescents in their Case 3, and Friedman, Grayzel and Lederer (1942) described a proliferation of the parietal layer of Bowman's capsule, giving a crescent-like appearance, as an occasional finding in infants of average age 2·7 months in the absence of evidence of any inflammatory reaction in the kidneys.

If it be accepted that crescents do not necessarily mean glomerulonephritis, then, as suggested by Claireaux and Pearson (1955), many cases described previously as neonatal glomerulonephritis may well have been cases of chronic pyelonephritis. Recent examples are the cases described by Thompson (1951), Collins (1954) and Kunstadter and Rosenblum (1954).

Possible Role of Congenital Abnormalities of the Nephron. Once past the neonatal period, boys seldom develop pyelonephritis except as a complication of some manifest urinary tract anomaly. All the infants in the present series were males but none of them showed any such anomaly. The possibility arises that a defect of the nephron, presumably congenital and demonstrable only microscopically, might be the predisposing lesion in these infants. The assessment of this possibility is complicated by the fact that kidneys from young infants dying of various diseases frequently show glomeruli and tubules which are 'sclerosed', immature or otherwise atypical. The cause and significance of these abnormalities is not clear. Friedman *et al.* (1942) have given the name 'congenital glomerulosclerosis' to the hyaline changes in the glomerular tufts and Bowman's capsule which were first described by Herxheimer in 1908. Friedman found these lesions in 12 out of 100 consecutive infants dying under the age of 14 months; he pointed out their relationship to obliterative changes in the corresponding afferent arteriole, but could advance no more fundamental explanation for their occurrence. It is interesting that the lesions were found about three times as often in males as in females, this being the estimated ratio of pyelonephritis in males to females in the first few months of life.

Marshall (1953), in a series of kidneys from infants and children, described structures which, on morphological grounds, he believed to be persisting foetal glomeruli and tubules. In most of the older infants and children pyelonephritis was present and Marshall suggested that such infections had as their underlying lesion a focal or localized dysplasia of the renal parenchyma.

In four cases of the present series (Nos. 1, 2, 3 and 4), Dr. E. M. Darmady and Miss Fay Stranack have shown by painstaking microdissection of the

kidneys that the nephrons were abnormal. In Cases 1, 2 and 3 the findings were reminiscent of the state of affairs in the immature nephrons seen in the kidneys of premature babies. It is to be noted that two patients in whom these atypical nephrons were found were brothers; this provides circumstantial evidence for the view that the lesions are congenital but at the same time makes it unjustifiable to draw conclusions from what may be a special case about the relationship of such lesions to neonatal pyelonephritis in general. Nevertheless, it remains an attractive hypothesis that these or other not easily recognized congenital abnormalities of the nephron may play an important role in predisposing certain babies to renal infection.

The Outcome of Neonatal Pyelonephritis. The majority of infants who develop an attack of acute pyelonephritis apparently recover. In a few cases, however, the renal disease may smoulder on, ultimately to cause hypertension, bone lesions, renal failure, or a combination of these. The proportion of cases in which this happens is unknown, and may be higher than is generally suspected. All four cases of chronic pyelonephritis in the present series showed left ventricular hypertrophy of varying degree and renal arteriolar lesions. This suggests that these cases were probably hypertensive, although only in Case 3 was hypertension actually demonstrated during life. The histological changes found in the kidneys closely resemble those described in many cases of 'renal rickets'. This lends support to the view expressed by Weiss and Parker (1939) that the great majority of infants and children who show so-called chronic interstitial nephritis associated with dwarfism and bone changes are in reality examples of long-standing chronic pyelonephritis.

In the light of these observations we would reinforce Stansfeld's plea for the consideration of pyelonephritis as a possible diagnosis in any infant who vomits, loses weight or goes off his food. Furthermore, we would urge that known cases of pyelonephritis should be followed up with the utmost care, and that apparently minor abnormalities of their urine should not be too readily disregarded.

Summary

Five cases of neonatal pyelonephritis in male infants are described. All the babies died before they were 5 months old and the necropsy findings are reported.

The kidneys in four cases showed changes believed to be those of chronic pyelonephritis. The appearances differed from those usually found in older children and adults with chronic pyelonephritis in that asymmetrical contraction and coarse shallow scarring were absent and crescents in varying numbers were prominent.

Microdissection of the kidneys from four patients, two of whom were brothers, showed abnormalities of the nephron.

We are grateful to Dr. R. Lightwood, Dr. T. Pearse Williams and Dr. T. Stapleton for permission to report on patients under their care; to Dr. J. L. Hamilton-Paterson, Dr. E. D. Hoare and Dr. P. L. Masters for permission to use material from Cases 2 and 4; to Dr. E. M. Darmady and Miss Fay Stranack for kindly undertaking the kidney microdissections; and to Professor Pryce and Dr. R. Lightwood for help with the manuscript.

We are grateful to the Hon. Editors of the *Proceedings of the Royal Society of Medicine* for permission to publish Fig. 4.

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THE MORBID ANATOMY OF INFANTILE MALNUTRITION IN CAPE TOWN

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(RECEIVED FOR PUBLICATION APRIL 9, 1956)

In recent years several detailed descriptions have been published of the morbid anatomical findings in malnourished children. Waterlow (1948) reported fatty liver disease from the West Indies and suggested that the children died from hepatic failure, while Hill (1951), working in the same area, described the condition of serous hepatosis. Davies in discussing kwashiorkor in Uganda (Trowell, Davies and Dean, 1954) felt that atrophy of the pancreas and other enzyme-secreting glands was the most important aspect of the condition, while the type of malnutrition seen in Johannesburg is still regarded as infantile pellagra by Gillman (Gillman and Gillman, 1951; Gillman and Gilbert, 1954). As a result of these papers one has an impression of several somewhat distinct pathological forms of malnutrition occurring in different parts of the world. These apparent distinctions, however, largely reflect differences of terminology and interpretation rather than of pathological findings, which, with the exception of those described in serous hepatosis, present a fairly constant pattern of retarded growth, fatty liver, pancreatic atrophy and skin lesions. The findings to be presented in this paper deviate only in their detail from this general pattern.

Apart from these regional differences, various clinical forms of malnutrition have been recognized and include kwashiorkor or its local equivalent, simple nutritional oedema, marasmus, paedatrophy and others. Although a clinical distinction between kwashiorkor and marasmus is made in Cape Town, chiefly on the absence of oedema in marasmus, a preliminary study of the material to be reported here showed that pathological distinction between these conditions was not feasible and in this paper they will be regarded as essentially similar expressions of the single entity of malnutrition.

No attempt will be made to cover the vast literature dealing with infantile malnutrition: this has been done by the authors already cited and by the many others included in their bibliographies.

Material and Methods

Post-mortem material was studied from 40 coloured and native children who suffered clinically from malnutrition. Adequate control material was available and was examined with particular care in six cases. Malnourished children suffering from any form of tuberculosis were excluded from the series.

For the purposes of this paper a coloured person is one of mixed blood with native, Hottentot and European as the chief elements, and a native is a member of one of a number of pure tribes native to southern Africa. Among the 40 malnourished children were 10 Natives, 30 Coloureds (23 males and 17 females) and the ages ranged from 4 to 30 months with an average age of 13 months.

All material was fixed in formol-saline for 24 to 48 hours ; frozen sections were stained with Sudan IV in Herxheimer's solution and paraffin sections with haematoxylin and eosin, van Gieson's stain, by silver impregnation methods for reticulum fibres and for the Prussian blue reaction with free iron.

Morbid Anatomical Findings

The great majority of children were in a state of poor general nutrition when they came to necropsy. There was an obvious loss of subcutaneous fat and a decrease in muscle mass that varied from moderate degrees of wasting to extreme emaciation. There were, however, a few exceptions as four of the children were well nourished, a fifth with gross oedema was described as not obviously wasted, and in one other child the fat depots in the limbs were well filled though adipose tissue was absent from the abdominal wall.

The detection of oedema at necropsy was sometimes hampered by chilling of subcutaneous tissues during the body's refrigeration, and even in fatal cases oedema present on the child's admission to hospital sometimes disappeared during treatment. For what the post-mortem observations are worth, however, oedema was recorded in 15 children. Ten children showed serous effusions and two of them, both peritoneal, were considerable in amount.

Twenty-two children showed some form of skin rash. There was a good deal of variation in the extent of the lesion in different children; its form varied and there was no typical distribution, virtually any part of the body being affected. The changes were not confined to the exposed areas of the body nor were they even more severe there. When the lesion was well developed it showed as a a brown to blackish hyperpigmentation with fine or coarse scaling, which with desquamation led to depigmentation. Ulceration occurred and was commonest on the pinnae of the ears and around the perineum. Purpura was present in addition to a typical skin rash in four children and was recorded in the absence of other skin changes in two children. Convincing evidence of a haemorrhagic tendency was not found elsewhere in the body in these children with purpura. Angular stomatitis was recorded in 10 children and moniliasis of the upper respiratory and upper gastrointestinal tracts in three. Microscopy of the scaling pigmented lesions showed parakeratosis, some degree of hyperkeratosis and thinning of the Malpighian layer with atrophy of hair follicles and sebaceous glands. Pigmentation was due to melanin which was found both in basal and upper layers of the epidermis and abundantly in the hyperkeratotic and parakeratotic layers.

A fatty liver has been a constant feature in descriptions of infantile malnutrition except for the report by Walters and Waterlow (1954) from West Africa. In this series some degree of fatty change was seen microscopically in 37 of the 40 children. The colour of the liver at necropsy varied from pale yellow to bright orange, the deeper shades being presumably partly contributed by bile, for one has noticed that many fatty livers from cases of malnutrition develop a green mottling after 24 hours' fixation in formalin. The most severely fatty livers floated in water and those slightly less affected floated in formol-saline. 'Floating livers' were present in 13 children. Microscopically, the severest grades of fatty change showed every cell or practically every cell in the liver lobule greatly distended by a large fat globule, so that the section resembled adipose tissue. This severe form of fatty change was present in 23 children. At the other extreme were those livers where only a minority of cells in a lobule were completely occupied by a single large fat droplet, and the degree of change was modest or slight. Livers of this type were found in eight children while intermediate moderately severe grades of fatty liver were found in six. Where fatty change was slight or moderate the process was usually but not invariably more marked peripherally and this distribution did not appear altered by the presence of infection. In two children the fat vacuoles were either so small or scanty that the sections did not justify the diagnosis of fatty liver and in a third fatty change appeared completely lacking.

Free iron pigment was not seen in more than trifling amounts in any liver section.

Small numbers of bile plugs were seen in 10 cases, and in one child several cells in each lobule were filled with bile. This particular child was jaundiced terminally with a serum bilirubin level of 1·9 mg. % and disturbed liver function tests.

Increased cellularity of portal tracts was noted in seven livers and was pronounced in three livers showing focal necrosis. Necrosis was seen in four livers, three of them with severe grades of fatty change. In two children the focal necroses were small and scanty but in the other two the process was more widespread and involved occasionally as much as half a liver lobule in a single necrotic focus. In all four livers the necrosis appeared very recent and was represented chiefly by granular cytoplasmic and nuclear debris among large pools of fat. In one case regenerative activity was suggested by multinucleate cells on the edges of the portal tracts. In none was it possible to demonstrate organisms or parasites. In one other very fatty liver large pools of fat had formed in many liver lobules and resembled the fat cysts described by Hartroft (1950), though they were larger and there were more of them than in his series.

The changes of serous hepatosis (Hill, 1951) were completely absent from these livers.

Silver impregnation methods showed loss of bridging reticulum fibres in fatty livers. This accentuated the length of portal tracts, which happened to be cut longitudinally, but a convincing monolobular fibrosis was never seen and portal cirrhosis was certainly absent. In two livers the portal tracts were unusually bulky in reticulum preparations and short thick processes entered the parenchyma from the portal triads while there was an excessive quantity of collagen in the walls of some central veins. These abnormalities of reticulum pattern were not seen diffusely throughout either of the two sections but only in subcapsular areas and were interpreted as secondary to focal subcapsular atrophy rather than as true fibrosis. Minor variations in the number, thickness and situation of the reticulum fibres were commonly seen but could be found in control material. In the four livers with focal necrosis, changes in reticulum pattern, apart from those secondary to fatty change, were uncommon and slight in degree while the same was true of the liver with the large pools of fat unassociated with cell necrosis.

Significant histological changes were commonly seen in the pancreas though alterations in the naked-eye appearances were not recorded. Microscopical sections were available from 34 children, and in 28 of them there was atrophy of the acinar cells though not of the islet tissue. In the severest grades of atrophy the cells were represented virtually by bare nuclei alone and this was seen in 17 children. In two of these 17 children the condensation of existing connective tissue was pronounced, but in only one child was there a true fibrosis and here, unlike in all the others, duct obstruction and inflammation were seen though evidence of fibrocystic disease of the pancreas was lacking. On histological grounds it seemed clear that the fibrosis was not secondary to simple atrophy with collapse of the pre-existing connective tissue framework of the gland. It was not, however, possible to infer that the pancreatic changes had preceded those in the liver in this particular child. One further microscopical change noted in the pancreas in nine children was the presence of pale pink-staining material in somewhat distended acini. This change corresponds to what Bodian (1952) describes as pancreatosis and what Emery (1951) found in many normal infant pancreases.

The commonest finding in the bones of these children was depressed endochondral ossification,

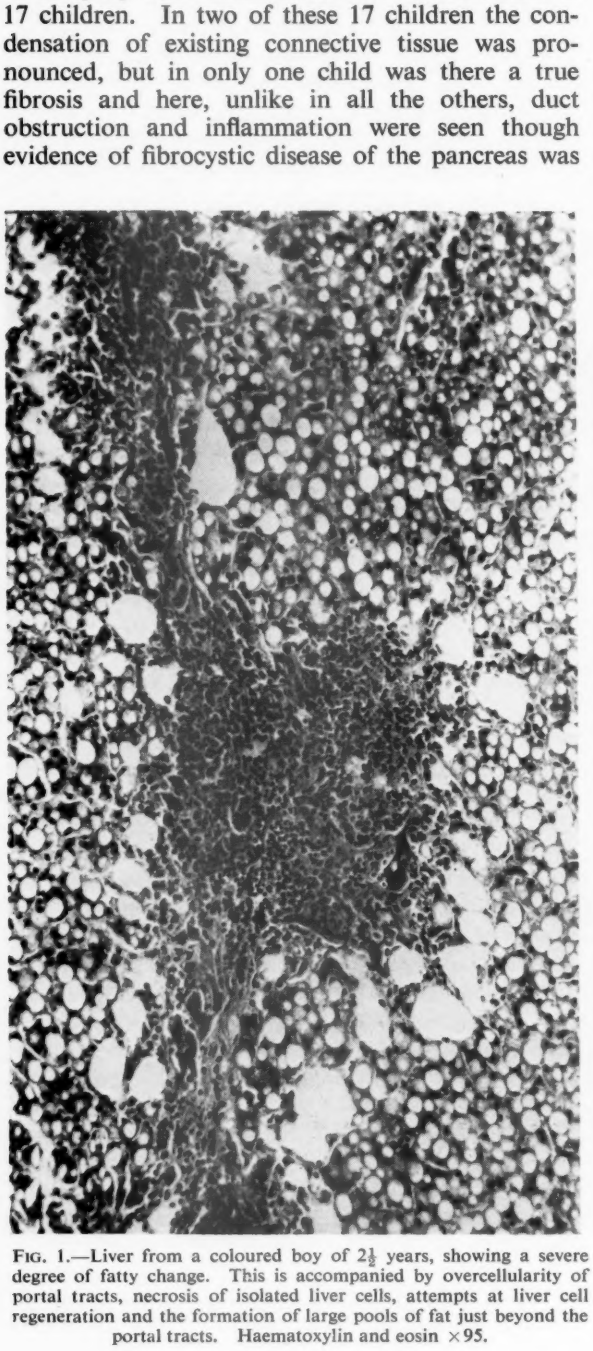

FIG. 1.—Liver from a coloured boy of 2½ years, showing a severe degree of fatty change. This is accompanied by overcellularity of portal tracts, necrosis of isolated liver cells, attempts at liver cell regeneration and the formation of large pools of fat just beyond the portal tracts. Haematoxylin and eosin ×95.

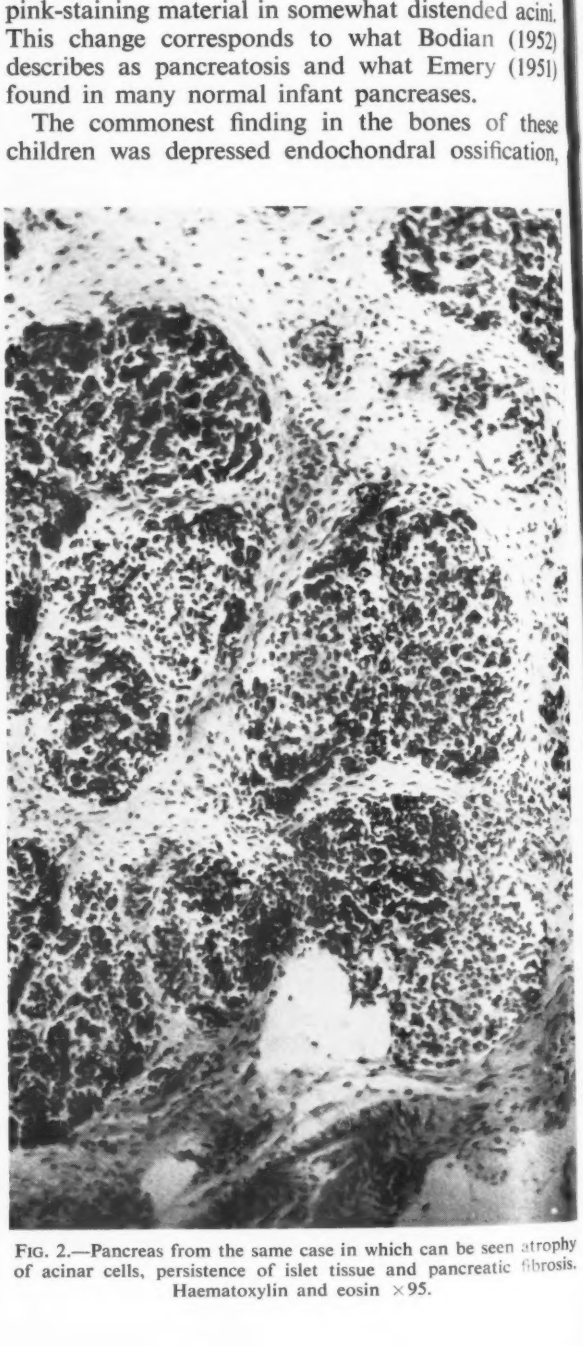

FIG. 2.—Pancreas from the same case in which can be seen atrophy of acinar cells, persistence of islet tissue and pancreatic fibrosis. Haematoxylin and eosin ×95.

and microscopical evidence of this was obtained in eight of the 12 children from whom sections were available. Swollen costochondral junctions were noted at necropsy in two children but changes compatible with rickets were present in only one of these. In the other there was abnormal vascularization of a bulky zone of hypertrophic cartilage cells and small foci of woven bone formation within this zone. A thin subperiosteal haemorrhage was present in the one other case but the histological features were otherwise normal and the clinical data did not suggest scurvy. Gelatinous degeneration of bone marrow was seen in two cases.

Skeletal muscle was available for study in 15 cases. Abnormal features were atrophy of muscle fibres in six and sarcolemmal nuclear proliferation in five cases. Diaphragmatic muscle was available in eight of these 15 children and in four sarcolemmal nuclear proliferation was again present. Lingual muscle was studied in 17 cases and the same nuclear changes were seen in five of them. Although the body muscles doubtless became depleted of protein in malnutrition one could never be sure how much of the microscopical picture was produced by the atrophy of disuse.

No significant changes were observed in the heart, endocrine organs or lymphoid tissue apart from accidental thymic involution in six cases where the thymus was described. Failure of foetal adrenal cortex to involute was not noted in any child.

One group of important changes remains to be described and will be considered under the heading of infections. In 31 of the 40 children the lungs showed microscopical evidence of pyaemic abscess or bronchopneumonia with or without abscess and pleurisy. Bacteriological examination was done on four occasions, and the organisms isolated were staphylococcus, pneumococcus, coliforms and proteus. Despite the frequency with which gastro-intestinal disturbances were recorded in the clinical histories (85%), naked-eye lesions in the bowel were uncommon and ulceration was seen only twice. Faeces was cultured from seven children at necropsy, Salmonella group E was isolated from two and no pathogens were found in the other five. Pyaemic abscesses were found in the kidneys of three children at necropsy and in three others the features were those of pyelonephritis. Kidneys not affected by inflammation were sometimes described as pale and a few as having a yellow tinge, the latter contributed presumably by lipoid since fat was seen in the convoluted tubules in frozen sections from three children. Glomeruli in various stages of hyalinization were often seen in this series of children but their number and situation were not different from what is regarded as a natural phenomenon at this age (Morison, 1952).

Discussion

When the pathological features of malnutrition in Cape Town are compared with those reported from other centres two differences are apparent. The first is the absence of serous hepatosis, which appears to be a distinct and separate entity. The second is the frequency and importance of infections in fatal cases of malnutrition in Cape Town. Necropsy experience appears to indicate quite clearly that infections precipitate the malnourished child into serious illness, determine the admission to hospital and are largely responsible for the high mortality in this condition. It is surely significant that in this series of 40 children there were only seven in whom an adequate cause of death could not be found, and in some of these, though the clinical history suggested an infection, the necessary bacteriological investigations were not available. This frequency of infections is not unique in Cape Town (Waterlow, 1948; Véghelyi, 1950; Trowell *et al.*, 1954) but nowhere has this feature been admitted as an essential part of malnutrition as seen in the hospital or the necropsy room.

Those aspects of malnutrition which have received greater attention are fatty liver and pancreatic atrophy. Fatty change in the liver is now well established as an accompaniment of infantile malnutrition but the functional significance of this change appears far from settled. Altmann (1948) believed that the evidence was insufficient to prove that fatty change seriously interfered with the liver's functions. Waterlow (1948) on the other hand, on the basis of abnormal bromsulphthalein retention and in the face of serum bilirubin levels not in excess of 1·8 mg. % believed that children with fatty liver disease died from hepatic failure. The diagnosis of hepatic failure, however, should be reserved for those cases which show microscopical evidence of widespread liver necrosis, and it was therefore withheld in the one case in this series where jaundice was present. There is clearly no justification for regarding the focal necroses seen in a few of the livers in this series as evidence of hepatic failure.

Examination of the available material produced no evidence that cirrhosis develops during the course of fatal malnutrition at this age nor were there indications that any focal necrosis would be followed by fibrosis, though frequently repeated lesions of this type might presumably have more serious consequences. Reticulum preparations, on the other hand, showed that appearances resembling

fibrosis could be produced by subcapsular atrophy, and since liver biopsy specimens often contain tissue from subcapsular areas, ignorance of this possibility might prove misleading.

So far as pancreatic atrophy is concerned, this paper fully confirms the views of Véghelyi (1950), Waterlow (1948) and Davies (1948) that acinar atrophy is a common accompaniment of malnutrition, but the pathological findings do not indicate how this lesion may be linked with the mode of death. There is, moreover, evidence from analysis of duodenal and intestinal secretions that proteolytic ferments at least are still produced by the pancreas in malnutrition (Altmann, 1953). No child in this series showed evidence that simple atrophy of acinar tissue leads to pancreatic fibrosis, while Emery's study of the normal infant's pancreas indicates that considerable caution is required before venturing the diagnosis of pancreatic fibrosis in infants.

Although this investigation cannot add or detract materially from the views held at present on the parts played by the liver and pancreatic lesions in malnutrition, it has shown that infections are of considerable importance in this condition. No one would claim that infections are a cause of malnutrition, but they do in Cape Town appear to be the most important single factor responsible for turning a badly nourished child, not obviously ill, into one so ill that careful hospital treatment is necessary if a fatal outcome is to be avoided.

One last finding needing explanation is the virtual absence of fatty change in the livers of two children and its complete absence in a third. This feature has been encountered by others and explained as the result of treatment, very prolonged periods of malnutrition, the occurrence of both malnutrition and undernutrition in the same child or as a feature of the earliest stages of malnutrition (Waterlow, 1948; Trowell *et al.*, 1954). One or more of the causes enumerated was found to apply in each of the three cases in this series that showed minimal amounts of fat in the liver.

Summary

The morbid anatomical findings in malnutrition in infants in Cape Town were found to be basically similar to those reported from other parts of the world, except that the condition of serous hepatosis was not seen.

Infections were thought to be an important precipitating factor in causing serious illness in malnourished children and the major factor in determining death.

I wish to acknowledge the help and encouragement given by Professor J. G. Thomson in the preparation of this paper.

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ACUTE NECROTISING RHEUMATIC ARTERITIS IN A CHILD

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(RECEIVED FOR PUBLICATION APRIL 13, 1956)

It has for some time been known that acute rheumatism does not affect only the heart but may produce lesions elsewhere in the cardiovascular system as well as in the joints, subcutaneous tissues and central nervous system. In the aorta, the disease process usually begins in the adventitia and only rarely extends beyond the outer third of the media. In the case to be described there was marked change in the intima, not only of the aorta but of the pulmonary arteries.

Case Report

The patient, a boy aged 7, was admitted to the wards of Dr. J. H. Hutchison at the Royal Hospital for Sick Children, Glasgow. The history was that of normal birth, infancy and early childhood. Tonsillectomy had, however, been done at the age of 5, because of recurring attacks of tonsillitis. Thereafter the child had remained well until about one year before death. He then began to show loss of appetite, increasing pallor and occasional bouts of fever. He was seen by the family doctor who noticed a heart murmur. On admission he was a pale, poorly nourished boy with a pulse rate of 160 per minute. Systolic and diastolic murmurs were heard at all areas. Blood culture on three occasions was sterile. The E.S.R. was 54 per hour and the tuberculin reaction negative. Despite intensive therapy death occurred suddenly.

Necropsy. The body was that of a poorly nourished boy of body length 1·2 metres. Subcutaneous nodules were palpable over the right elbow posteriorly, over the occiput and the dorsal spine. There was no other external evidence of disease. Dissection showed no significant abnormality of the peritoneum, gastro-intestinal tract, gall-bladder, pancreas, adrenals, kidney, ureters, bladder, prostate and testes. The liver (1,000 g.) and spleen (100 g.) were markedly congested. The cranial cavity, meninges, brain (1,380 g.), pituitary, thyroid and thymus glands showed no features of note. There were recent tenuous adhesions between the parietal pericardium and visceral pleura but no pleurisy or pleural effusions. The lungs (each 280 g.) showed only a few small scattered haemorrhagic areas deep in the substance of both upper lobes.

The pericardial cavity was completely obliterated by oedematous fibrous adhesions. The heart weighed 325 g. and was much enlarged in the transverse diameter. The right auricle and ventricle were hypertrophied and dilated with relative incompetence of the tricuspid valve. The pulmonary valve appeared normal. The left ventricle appeared normal but the left auricle was somewhat dilated. There was neither stenosis nor obvious incompetence of mitral and aortic valves. Both of these, however, showed some oedema of the cusps and along the lines of contact of the cusps of both valves were numerous tiny translucent typical rheumatic vegetations. There was moderate subendocardial thickening of the left auricle but no macroscopic change in the great vessels or coronary artery orifices.

Histological Examination. There was evidence of mild respiratory infection with foci of collapse in the lungs which showed neither hyaline membrane nor abundant haemosiderin-containing macrophages. The gastro-intestinal tract, pancreas, salivary glands, adrenals, kidneys, lymph nodes, cerebral cortex, medulla oblongata, thyroid, pituitary, testes, prostate, breasts and sympathetic ganglia showed no significant abnormality of parenchyma or of blood vessels. The liver and spleen showed congestion only.

Well formed Aschoff bodies were seen in the endocardium of the left auricular appendage, left auricle and left ventricle (Fig. 1). There were also diffuse inflammatory infiltrates which included some polymorphs. An organizing pericarditis was also noted. Scanty, ill-formed Aschoff bodies were noted in the myocardium of the right auricle only. There were no endocardial Aschoff bodies in any chamber on the right side but an organizing pericarditis was again evident. The aortic valve cusps were thickened and the presence of organizing surface vegetations was confirmed. The mitral valve cusps were also thickened, a little fibrosed and vascularized and showed surface vegetations (Fig. 2). Aschoff bodies were very numerous in McCallum's area.

Blood Vessels. Longitudinal section through the aorta showed that just distal to the left coronary ostium there was obvious intimal thickening with an infiltrate of lymphocytes and larger darkly-staining histiocytic cells. On section a little distal to this the adventitial coat was oedematous with congestion of the small nutrient vessels.

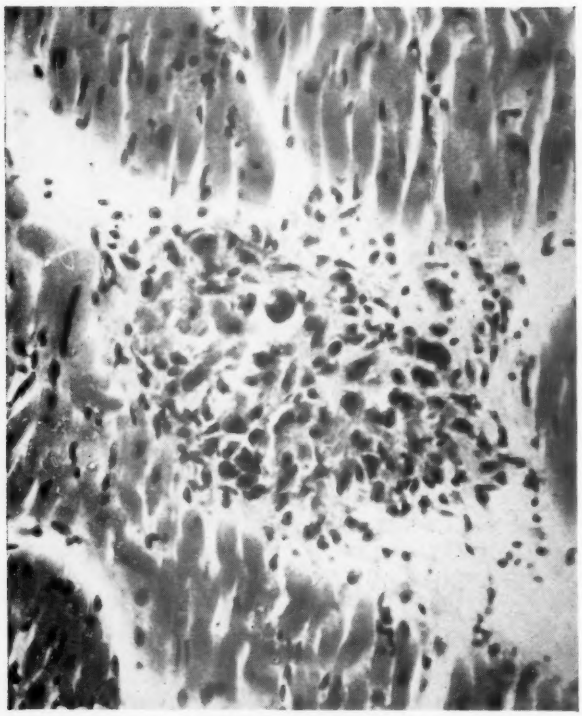

FIG. 1.—An Aschoff body is seen in the connective tissue of the myocardium of the left ventricle. Haemalum and eosin ×280.

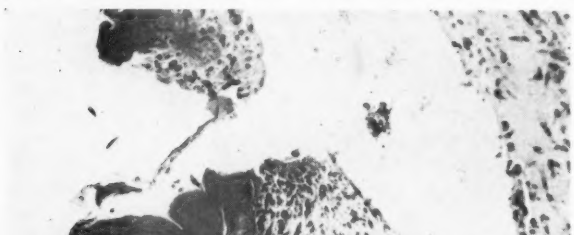

FIG. 2.—Mitral valve cusp showing thickening and increased cellularity with vegetation. H. and E. ×110.

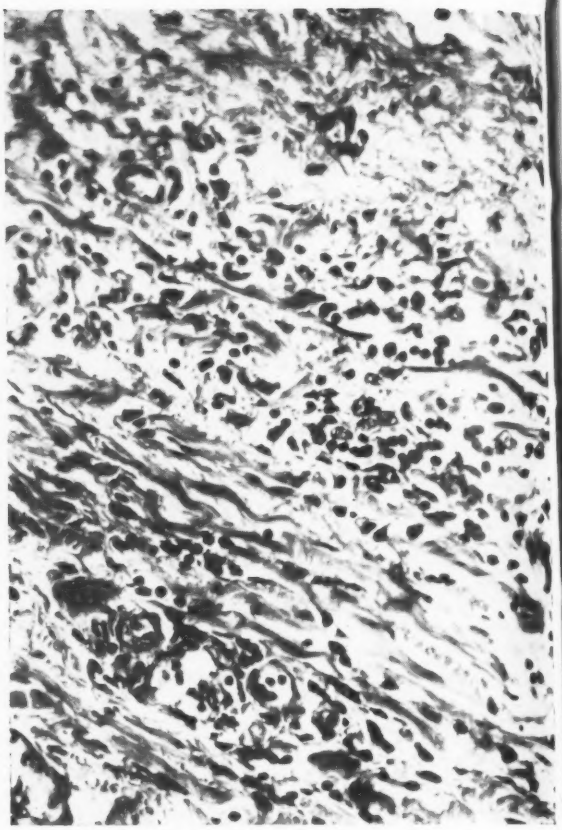

FIG. 3.—In the adventitial coat of the thoracic aorta there is a marked infiltration by mononuclear cells. Masson. ×280.

FIG. 4.—The intima of the thoracic aorta shows very severe fibrinoid necrosis of the internal elastic lamina with a large number of polymorphs in the subendothelial tissue. Masson. ×280.

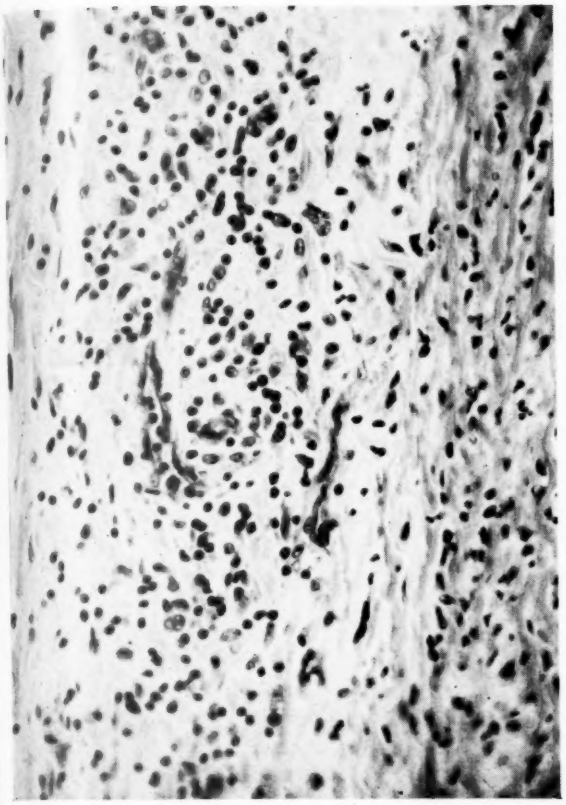

FIG. 5.—The adventitial coat of the abdominal aorta shows a well-established infiltrate of lymphocytes and histiocytes around the vasa vasorum. H. and E. ×280.

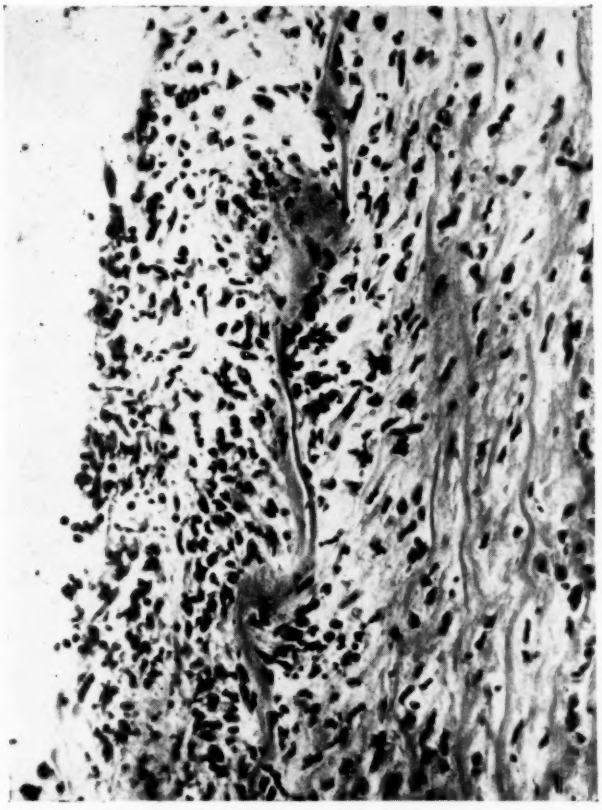

FIG. 6.—There is a thickening and fibrinoid change of the internal elastic lamina of the abdominal aorta. The intima is infiltrated by polymorphs, many of degenerate appearance. The endothelium has been lifted and in some places has disappeared. H. and E. ×280.

Around these, but also scattered diffusely throughout was a cellular infiltrate consisting of lymphocytes, scanty plasma cells and eosinophil polymorphs as well as occasional darkly-staining histiocytic cells (Fig. 3). The media showed only slight oedema while the intima was somewhat thickened and pale-staining, with nuclei of rather stellate appearance.

Further distal still, the medial coat again showed some oedema. The intima was markedly affected in a sector representing about one twelfth of the circumference and placed laterally. The maximum increase in thickness of the intima here represented one-half the thickness of the media at this point. Much of the increase in thickness was due to collagen fibres with fibroblastic nuclei. The most striking feature, however, was the great destruction of the internal elastic lamina. This showed increasing fragmentation towards the centre of the lesion, the dull fuchsinophil crimson-red staining appearance contrasting with the bluish-pink of the unaffected elastic tissue of the media as shown by Masson's stain (Fig. 4). Towards one end of the affected section there was a short length where the immediately subintimal elastic tissue showed a similar fibrinoid change. There was a well-established polymorph infiltrate most highly developed where the fibrinoid appearance was present. Over the affected portion the endothelium was rather lifted, possibly due to the infiltration of inflammatory cells.

Abdominal Aorta. Section at several different levels showed in the adventitial coat perivascular round cell infiltrates, mainly lymphocytic but with occasional plasma cells and histiocytes (Fig. 5). The medial coat showed some oedema with occasional scanty lymphocytes and histiocytes around the vasa vasorum. The appearances in the intima varied from simple thickening of the layer, which was pale-stained and showed some lymphocytic infiltration, to one of profound structural alteration. The latter appearances resembled closely those described above in the thoracic aorta. The affection was again sectoral but occupied about one-quarter of the circumference of the lumen. The intima was thickened, pale and consisted of two layers of collagen. Towards the media the fibres were well-formed and the cells fibrocytic in character but towards the lumen they were finer, immature and associated with fibroblastic cells. Between these distinct layers a well-formed elastic lamina distinct from the definitive internal lamina showed fibrinoid change and was surrounded by polymorphs which were also present in lesser number in the

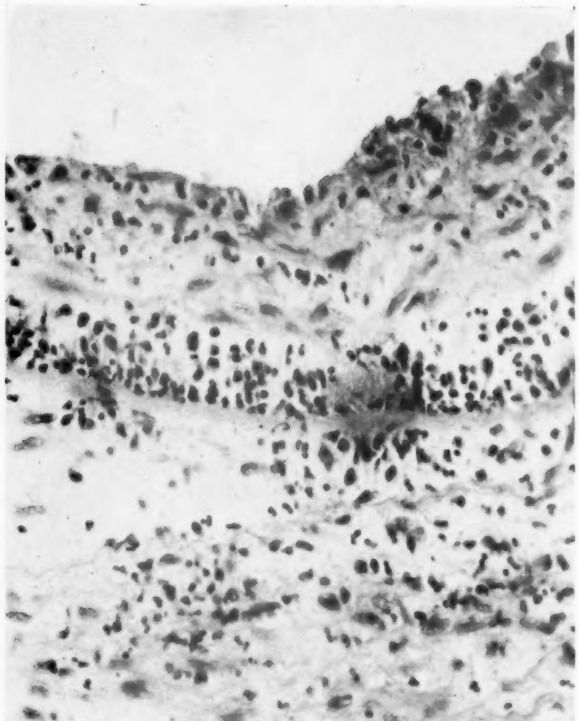

FIG. 7.—A major branch of the pulmonary artery showing less severe arteritis. An early polymorph infiltrate extends into the intima. H. and E. ×280.

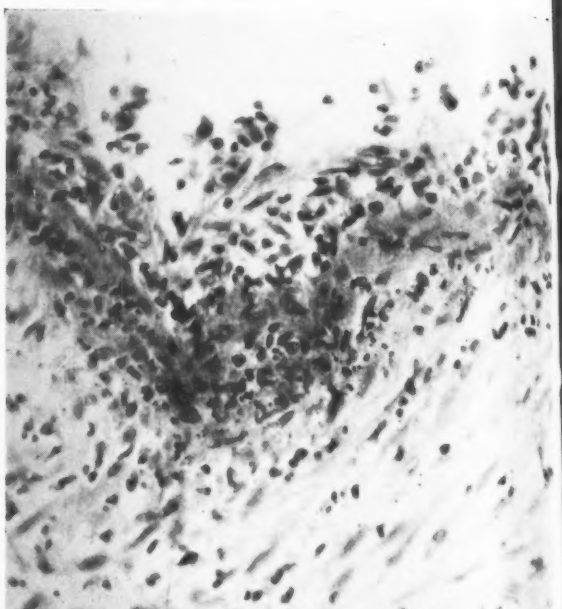

FIG. 8.—A major branch of the pulmonary artery closely adjacent to that seen in Fig. 7. The fibrinoid change in the internal elastic lamina is quite severe and the inflammatory reaction is well marked. H. and E. ×280.

intima towards the lumen (Fig. 6). This fibrinoid change was not of equal severity along the entire length of the recently formed elastic lamina. The endothelium was again raised by the inflammatory infiltrate.

Subclavian Artery. The adventitia showed some simple round cell infiltration; the media slight oedema, while the intima was pale and a little thickened. In the major branches of the subclavian artery occasional lymphocytes and histiocytes were seen in the adventitia but no other abnormality was noted.

Coronary Arteries. There were no significant changes in the major vessels.

Pulmonary Arteries. The major arteries showed well marked aggregates of round cells in the adventitia, mainly around the vasa vasorum. Also present were occasional plasma cells, some binucleate. Scanty round cells were also seen in the media around the vasa. Also present in the media were occasional polymorphs scattered throughout the outer aspects of the coat. These were present only in that sector of the artery in which the intima was affected. This intimal change consisted of severe damage to the internal elastic lamina, which was thickened and granular with very numerous polymorphs present on that side adjacent to the lumen with fewer on the medial side. Many of the polymorphs appeared quite degenerate (Figs. 7 and 8). In the lung substance the major branches only of the pulmonary artery were also affected. Here again the internal elastic lamina showed an appearance of fibrinoid necrosis with numerous polymorphs associated with the damaged tissue. In the adventitia round cell infiltrates were noted surrounding the vasa.

Superior Vena Cava. This showed scanty round cells in the adventitia coat around the vasa with perhaps slight thickening of the intima.

Inferior Vena Cava. In the thoracic portion this showed scanty lymphocytes and histiocytes in the adventitia with slight thickening of the intima also. In the abdominal portion slight intimal thickening was the only abnormality.

Pulmonary Veins. Apart from scanty round cell infiltrates in the adventitia no abnormality was seen. The pulmonary veins in the substance of the lung showed no abnormality.

Coronary Vein. One small coronary vein showed a sectoral change with an infiltrate of polymorphs and plasma cells in the subintimal zone.

Discussion

The effects of acute rheumatism on the walls of arteries are briefly described in most standard text-

books, e.g., Cappell (1951). Such lesions, although most often found in the aorta, may also occur in smaller vessels. In the aorta the lesions are said to begin in the adventitia and consist of infiltration by lymphocytes and plasma cells. Here and there foci may be noted where there is a marked histiocytic reaction and typical Aschoff bodies may form. This cellular infiltration sometimes spreads to the media and may lead to absorption of elastic tissue but rarely extends further than the outer third of the medial coat. Of other vessels affected, the lesions are most often found in the smaller visceral arteries. They are of more acute character and may show some medial necrosis with leucocytic infiltration, somewhat resembling the lesions of polyarteritis nodosa although thrombosis and aneurysmal dilatation have not been observed.

Attention was first drawn to the occurrence of rheumatic aortitis by Pappenheimer and von Glahn (1924, 1926, 1927). In their first paper they drew attention to Aschoff bodies or cells in the aortic adventitia; in the second to affection of the media, where amphophilic cells were present along with polymorphs and round cells; and, in the third, differentiated rheumatic aortitis into two types, one with a perivascular reaction and another with diffuse reaction in the intima and subjacent media. Gray and Aitken (1929) described four cases where there was no evidence of syphilis or arteriosclerosis but a history of rheumatic fever, chorea or tonsillitis and in which there were old lesions of media and intima.

Kugel and Epstein (1928) studied 24 cases of active rheumatism and showed that in 17 instances Aschoff bodies or more often diffuse infiltrates containing large cells were present at the musculo-arterial junctions of the pulmonary arteries. In two cases there were macroscopic lesions of the intima of the pulmonary arteries, while in five there was histological evidence of intimal affection. In one instance there was actual fibro-elastic necrosis with an inflammatory infiltrate. The medial wall showed cellular infiltrates in five cases and the vasa vasorum were sometimes thickened. In 22 cases the aorta was also examined and Aschoff bodies were never found in the wall. Paul (1927, 1928), in reviews of pleural and pulmonary lesions in rheumatic fever, stated that while Aschoff bodies may be found in the main pulmonary arteries, the lesions in the moderately sized vessels are less specific while in the arterioles there may be a fairly marked periarteritis. Chiari (1930) also described lesions of the pulmonary arteries. Epstein and Greenspan (1941) detailed the appearances of the lung in so-called rheumatic pneumonia and conclude that there is a characteristic but not specific pulmonary picture. They describe arteritis of the pulmonary arteries in four out of 45 cases. These four occurred where death intervened at a second or later attack of acute rheumatism.

Von Glahn and Pappenheimer (1926) described inflammatory changes of exudative type in the peripheral vessels in rheumatism. Karsner and Bayless (1934) reviewed the literature of vascular changes in acute rheumatism including those in the aorta and pulmonary artery. They analysed carefully the appearances of the coronary arteries in 56 cases where the heart showed unequivocal Aschoff bodies and established the great frequency of affection of the coronary arteries in acute rheumatism as witnessed by fibrinoid change, necrosis, alteration in the elastic tissue, etc. Gross, Kugel and Epstein (1935) have also studied the coronary arteries in cases of acute and 'healed' rheumatic heart disease and concluded that some coronary lesions are so peculiar as to suggest the possibility of a specific rheumatic nature. Klinge (1930 and 1933) has also described in detail vascular change in peripheral vessels. Anderson (1953) summarized the appearances seen in the peripheral vessels. These lesions are not confined to the coronary arteries but may be seen in the lungs, pancreas, kidney, ovary, testis and skin. Histologically the entire thickness of the wall is affected and frequently the whole circumference. The endothelium is swollen, the media thickened by oedema and fibrinoid change, with damage to the internal elastic lamina. Not infrequently large arterioles show an exudative and necrotizing panarteritis. Musculo-elastic hyperplasia may greatly narrow the vessel lumen.

Shaw (1929) investigated the topography of lesions in rheumatic fever and stated that aortitis is most often seen in the proximal and not in the abdominal aorta. He further stated that while the pulmonary artery and its major branches may be affected, lesions are not seen in the intrapulmonary branches. Less specific lesions are described in the carotid, subclavian and renal arteries and in the superior vena cava.

Lendrum (1955) has recently discussed the changes in the pulmonary arteries in mitral stenosis and considers these to be an example of fibrinous vasculosis. This term, 'fibrinous vasculosis', is proposed for the essentially similar microscopic appearances in a group of disparate conditions which include infarction, malignant hypertension, polyarteritis nodosa, disseminated lupus erythematosus, dermatomyositis and thrombotic thrombocytopenia. He points out that in all the above-

mentioned conditions the fibrin is quite often seen under an intact endothelium; the change may be segmental or affect the entire circumference. The three forms of fibrinous vasculosis may be histologically indistinguishable, except so far as vessels of different calibre are involved in the different diseases. The concept of a fibrinous vasculosis as a form of exudation common to all diseases mentioned, depending on an upset between the pressure in the vessel and the permeability of the lining may, he thinks, help in our understanding of the peculiar diseases in which it occurs. Lendrum has seen in the lungs fibrinous vasculosis in cases of mitral stenosis, of primary pulmonary hypertension, of disseminated lupus erythematosus, of drug-induced arteritis and of infarction in a case of acute rheumatic disease. The lungs from the cases of mitral stenosis showed a more widespread and severe involvement of the vessels than was seen in any other condition. Lendrum believes that in cases with mitral valve stenosis it can be reasonably assumed that a state of pulmonary hypertension existed during life and that in such cases the fibrinous vasculosis can be related to hypertension, it being unnecessary to postulate a state of hyperergy.

In the present case it is probable that the earliest changes occurred in the adventitia since the disease process is limited to this layer in some of the vessels examined. Possibly in many instances the condition does not progress further but in others extends to the outer third of the media. The media was nowhere strikingly affected in the case described above but intimal changes were severe both in the aorta and larger pulmonary arteries, being similar to those described in peripheral vessels. Although Aschoff bodies were frequently seen in the heart they were invariably absent from the blood vessel lesions. The involvement of the abdominal portion of the aorta is contrary to the experience of Shaw (1929).

The lesions described above appear to be essentially of an acute necrotizing type similar to those seen in polyarteritis and related diseases. In the present case there was no established mitral stenosis and the condition is not the fibrinous vasculosis complicating pulmonary hypertension as described by Lendrum. In any case the involvement of the systemic blood vessels precludes this explanation. The condition almost certainly represents an aspect of the acute rheumatic process. The major changes are seen only in the arteries although the adventitia of the veins are also mildly affected.

Summary

Acute necrotizing arteritis is described in a 7-year-old boy who died of acute rheumatism. Both aorta and pulmonary artery showed severe changes. The condition is almost certainly part of the rheumatic process.

My thanks are due to Dr. J. H. Hutchison for permission to publish this case and Mr. W. Mason for technical assistance and for the photographs.

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LEAD POISONING IN CHILDHOOD TREATED BY THE SUBCUTANEOUS ADMINISTRATION OF A CHELATING AGENT

BY

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(RECEIVED FOR PUBLICATION APRIL 16, 1956)

The treatment of lead poisoning with the neutral calcium disodium salt of ethylene diamine tetra-acetic acid (calcium disodium E.D.T.A.) was first described by Bessman, Ried and Rubin in 1952. Since then there have been many reports testifying to the value of this treatment, including those of Sidbury, Bynum and Fetz (1953), Karpinski, Rieders and Girsh (1953), Byers and Maloof (1954), Bessman, Rubin and Leikin (1954) and Giles, Moore and Still (1955). The preparation is marketed commercially as 'versenate' and belongs to a group of chemical agents known as chelating agents, this term being derived from the Greek word meaning a 'claw'. Chelating agents are capable of combining with certain metals to form firm complexes called chelates which are stable ring structures, water soluble and readily excreted. In them the metal is not ionized and therefore does not show its usual chemical or physiological activity. The strength, or stability, of the chelate varies with different metals, and one metal which forms a stable complex may displace a second metal whose complex is less stable. This fact is the basis of the therapeutic use of calcium disodium E.D.T.A. in lead poisoning. The affinity of lead for E.D.T.A. is greater than that of calcium and so, when calcium disodium E.D.T.A. is administered, lead will displace calcium from this complex and a lead disodium E.D.T.A. chelate will be formed. This particular chelate is very stable and is readily excreted in the urine; in this way the circulating lead is safely removed.

It was pointed out by Bessman *et al.* (1954) that, if calcium disodium E.D.T.A. acted at maximum efficiency, an excretion of about 260 mg. of lead should occur after the intravenous administration of 0·5 g. of the drug. In fact, they observed that only 1·8 mg. of lead was excreted after this dose, representing an efficiency of only 0·7%. The probable reason for this low efficiency is that lead is bound in the tissues to sulphahydryl groups and, although the affinity of lead for calcium disodium E.D.T.A. is greater than for the sulphahydryl groupings, they are much more numerous in the tissues. Bessman *et al.* found that increasing the dose of calcium disodium E.D.T.A. did not produce a corresponding increase in the excretion of lead and they suggested that this was probably due to the rapid excretion of the drug in the urine before it could be brought into equilibrium with the tissues. Because of this, they suggested that the drug should be given either by slow continuous intravenous infusion or by repeated intravenous administration at six-hourly intervals. A majority of the published cases of lead poisoning treated with calcium disodium E.D.T.A. have been given the drug by the intermittent intravenous administration of a dilute solution (not exceeding 3% concentration). The drug has also been given orally (Bradley and Powell, 1954) but it is much less effective when administered by this route, and it may cause gastro-intestinal upsets.

Lead poisoning in childhood is almost entirely confined to children under 5 years of age. Tanis (1955) reported 33 cases; all of the children were aged less than 5 years and 70% of them were aged between 1 and 3 years. Mellins and Jenkins (1955) reported 21 cases with ages ranging from 10 months to 44 months. The usual cause of lead poisoning in childhood is the habit of chewing and eating paint from cribs, toys, furniture, woodwork or walls. The tendency to put things in the mouth, though normal in the first year of life, is considered abnormal if it is continued and it may then be referred to as a pica or perverted appetite. A history of pica was elicited in 94% of the cases reported by Tanis. Though lead paint is no longer used for interior decoration or for painting cots and toys, Gibb and MacMahon (1955) have pointed out that the amateur home decorator may believe that lead paints are the best paints and may apply them to internal surfaces and fittings.

The fact that lead poisoning in childhood is most common in the toddler age group gives rise to certain technical problems when calcium disodium E.D.T.A. is used in treatment. As already mentioned, it is usually recommended that the drug should be given by intermittent intravenous administration of a dilute solution. By this route, the maximum dose per hour should not exceed 0·5 g. per 30 lb., the maximum dose per day should not exceed 1 g. per 30 lb. and the maximum dose per week should not exceed 5 g. per 30 lb. Usually two courses of treatment are given, separated by a rest period of one week. Such a treatment schedule obviously involves repeated intravenous infusions and, in a plump toddler, it may be difficult to carry through the treatment without cutting down on veins.

So far, there have only been two references in the literature to the administration of calcium disodium E.D.T.A. by the subcutaneous route. Bessman *et al.* (1954) mention that the drug may be given in this way but do not discuss this method of administration in any detail. Kneller, Uhl and Brem (1955) described a case of lead poisoning in a child of 20 months; two courses of calcium disodium E.D.T.A. were given by subcutaneous clysis and the child made a complete recovery. No local reactions occurred.

Two further cases of lead poisoning in childhood, treated by the subcutaneous administration of calcium disodium E.D.T.A., are described here.

Case Reports

Case 1. This girl was aged 18½ months at the time of admission. She had not been well for about four weeks before admission with anorexia, frequent vomiting, constipation, intermittent abdominal pain and irritability as the main symptoms; convulsions had not occurred. During the three months before admission, the child had developed the habit of picking the paint off the inside of a window-sill and eating it. The father, who was a seaman, had painted the window-sill with a marine paint.

On examination, she looked pale and ill and it was evident that she had recently lost weight. Her weight was 21 lb. She was drowsy and extremely irritable. Apart from general muscular hypotonia, there were no other abnormal findings. There was no evidence of a lead line on the gums. Examination of the blood showed that the haemoglobin was 53% (7·9 g. %); punctate basophilia was present. *X*-ray examination of the wrist revealed dense lines in the bones suggesting the deposition of a heavy metal. The C.S.F. was clear and contained protein 70 mg. %, sugar 98 mg. %, and the test for globulin was positive; cells were less than 1 per c.mm. The urine contained a reducing substance, shown by chromatography to be glucose. Two-way chromatography revealed abnormal aminoacid ria; large amounts of glycine, alanine and serine, moderate amounts of taurine, threonine, histidine and β-amino-isobutyric acid, and small amounts of valine, leucine, tyrosine, cystine, lysine, aspartic acid and glutamic acid were present. Total serum protein was 5·8 g. %, with albumin 2·62 g. %, globulin 3·18 g. % and albumin: globulin ratio 0·82:1.

Treatment with calcium disodium E.D.T.A. was started three days after admission. It was decided to give the drug by the subcutaneous route because it was felt that intravenous administration would involve cutting down on several veins. A 1% solution of the drug was made up in normal saline (1 g. in 100 ml.) and 25 ml. (0·25 g.) was given subcutaneously every six hours for five days (a total dose of 5 g.). At first the solution was given by drip infusion but subsequently it was found more convenient to give it by slow subcutaneous injection from a syringe, taking about 30 minutes to give 0·25 g. Hyaluronidase (1,500 international units) was given with each injection of calcium disodium E.D.T.A. A rest period of seven days was allowed after the first course and this was followed by the administration of a second course of the drug (5 g.) over a period of five days. Absorption of the drug was rapid from the sites of injection and the solution did not appear to cause any local pain. A small staphylococcal abscess developed at the site of one injection; this was incised and healed satisfactorily.

The child's condition began to improve 24 hours after starting treatment. She was brighter and less irritable; vomiting was less frequent and she began to accept food for the first time since admission. Over the next few days she improved rapidly; the improvement in her appetite was particularly striking and vomiting ceased completely. No stool was passed during the first seven days in hospital; subsequently her bowels became regular. Further general improvement took place during and following her second course of treatment. Examination of the blood after the second course of treatment showed that the haemoglobin was 58% (9·6 g. %); punctate basophilia was no longer present. The C.S.F. was again examined and contained protein 30 mg. %, and sugar 82 mg. %; the test for globulin was negative and the cell count was 11 leucocytes per c.mm. (65% mononuclears). Chromatography of the urine showed that the amount of glucose was much less than before treatment; qualitatively there was still an abnormal aminoaciduria but the quantities of the amino-acids were much less.

The concentration of lead in the blood before treatment was started was 83 μg. %; after the completion of the second course of treatment the concentration was 50 μg. %. The urinary lead concentration was 280 μg. per litre before the start of treatment; on the second day of the first course it was 700 μg. per litre and, three days after the completion of the first course, it was 220 μg. per litre. (Normal values for lead in blood and urine are 10-30 μg. % and 30-80 μg. per litre respectively.)

During the convalescent period her appetite was voracious and she gained weight rapidly. Following a course of intramuscular iron ('imferon'), her haemoglobin rose to 80%. To date, she has been followed up

for a period of six months, during which time her physical and developmental progress has been normal. There has been no recurrence of pica. The lead lines are still present on *x*-ray examination of the bones but they are gradually diminishing in intensity.

Case 2. This boy was aged 23 months at the time of admission. Anorexia, frequent vomiting, constipation, loss of weight and irritability had been noted for about four weeks before admission. Convulsions had not occurred. For about four months before admission, he had been picking paint off the outside of a window-sill and eating it.

On examination, he was pale, irritable and thin. His weight was 22 lb. Physical examination was otherwise negative; no lead line was present in the mouth. On examination of the blood his haemoglobin was found to be 57% (8·5 g. %); punctate basophilia was present. *X*-ray examination of the wrists revealed dense lines at the ends of the bones, suggesting the deposition of a heavy metal. The C.S.F. contained protein 80 mg. %, sugar 105 mg. % and the test for globulin was positive; the cell count was normal. The urine contained a reducing substance, shown by chromatography to be glucose; small amounts of fructose and sucrose were also present. The test for coproporphyrin was positive. Two-way chromatography showed a greatly increased excretion of amino-acids, with large amounts of glycine, alanine, threonine and serine, moderate amounts of histidine, lysine and taurine, and small amounts of β-aminoisobutyric acid, cystine, valine, leucine, phenylalanine and tryptophane. Total serum protein was 7·1 g. %, with albumin 3·07 g. %, globulin 4·03 g. % and albumin:globulin ratio 0·75:1.

Treatment with calcium disodium E.D.T.A. was started two days after admission. The child's superficial veins were not prominent and it was therefore decided to give the drug subcutaneously as a 1% solution in normal saline, 25 ml. (0·25 g.) being given by slow subcutaneous injection every six hours for five days (a total dose of 5 g.). Each injection took about 30 minutes and hyaluronidase (1,500 international units) was given with each dose. A rest period of seven days was allowed after the first course and this was followed by the administration of a second course of 5 g., again over a period of five days. No local complications occurred.

The immediate clinical response was not as striking as in Case 1, although the boy's appetite gradually improved and his bowels became regular during the week following the start of treatment. After the second course of the drug improvement was more marked; his disposition was happier and his appetite was normal. His haemoglobin after treatment was 62% (9·2 g. %); punctate basophilia was absent. The C.S.F. contained protein 35 mg. %, sugar 62 mg. % and the test for globulin was negative; the cell count was normal. The reducing substance was no longer found on chromatography and the abnormal aminoaciduria was quantitatively and qualitatively much less than on admission.

The concentration of lead in the blood before treatment was 108 μg. %. Following the first course of treatment it was 200 μg. % but it had fallen to 87 μg. % five days later and before the start of the second course. Following the second course of treatment, it had fallen to 30 μg.%. The urinary lead concentration was 160 μg. per litre before the start of treatment; a figure of 344 μg. per litre was obtained after the first course and a figure of 206 μg. per litre after the second course.

The child improved steadily after discharge from hospital. His disposition was happy, his appetite was excellent and his bowels were regular. Pica did not recur. Iron therapy was not prescribed but, despite this, his haemoglobin was 83% (12·3 g. %) seven weeks after the date of admission to hospital. So far, he has been followed up as an out-patient for six months, during which time his developmental progress has been normal. The lead lines are still present in the metaphyses of the bones but they are gradually diminishing in intensity.

Summary

The theoretical basis of the use of calcium disodium E.D.T.A. in the treatment of lead poisoning is discussed.

The age incidence and the causes of lead poisoning in childhood are mentioned.

The difficulties associated with the administration of calcium disodium E.D.T.A. are described.

Two cases of lead poisoning in childhood, successfully treated by the subcutaneous administration of calcium disodium E.D.T.A., are described.

I should like to thank Professor N. B. Capon for his advice and criticism, Drs. F. P. Hudson and S. E. Keidan for permission to publish details of cases admitted under their care and Mr. J. T. Ireland for the biochemical investigations.

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A CASE OF ATRESIA OF THE LARYNX

BY

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(RECEIVED FOR PUBLICATION MARCH 20, 1956)

Congenital abnormalities of the larynx and trachea rarely cause death in the newborn. Milder anomalies are not uncommon and are compatible with survival. Holinger, Johnson and Schiller (1954) reported a series of 379 cases, of which 305 were congenital laryngeal stridor. Among 19 cases of congenital web of the larynx three required tracheotomy and none died. This condition may persist without symptoms into adult life. One case of membranous atresia of the glottis survived after immediate tracheotomy. Congenital subglottic stenosis was found in 34 cases, in two of which it was due to deformity of the cricoid cartilage. Fourteen of these required tracheotomy. One case of cartilaginous stenosis died at the age of 4 weeks in spite of tracheotomy. There were five cases of congenital cyst and 15 of laryngocoele. Congenital papillomata and tumours such as haemangioma and lymphangioma have been reported. Kessel and Smith (1953) described a case of congenital absence of the trachea and reviewed the literature on tracheal anomalies.

Subglottic cartilaginous atresia or stenosis is the least common anomaly. O'Kane (1936) described a case of stenosis which survived after tracheotomy and Baker (1954) reviewed the same case at the age of 18 years. Gunn (1926) referred to one case of partial and one of complete stenosis. Potter and Bohlender (1941) reported a case of atresia which died 20 minutes after birth and Potter (1952) referred to two other cases. Bizza (1941) described complete atresia in a stillborn infant with 'hyperplasia' of the lungs and referred to eight other cases in the German literature. Sayre and Hall (1954) reported one case of stenosis which survived for two days and one of atresia. They referred to 11 cases in the German literature. Sandison's (1955) case was associated with partial absence of the trachea and tracheo-oesophageal fistula.

Of the above cases complete cartilaginous atresia was present in six and membranous atresia in one. Bizza (1941) and Sayre and Hall (1954) mention a further 11 cases in the German literature. The purpose of this paper is to describe a case of cartilaginous subglottic atresia and to discuss the embryology, diagnosis and possible treatment.

Case Report

The infant was the first of girl twins delivered of a healthy mother two weeks before the expected date following an uneventful pregnancy. The previous obstetrical history consisted of two full-term normal babies and one miscarriage at three and a half months. The mother is Rh positive and has a negative Wassermann reaction.

At birth the child was very asphyxiated, cyanosed and did not cry. Oxygen was administered by face mask and an occasional gasp was observed, in spite of which the condition rapidly became that of asphyxia pallida. The apex beat was firm and regular. Lobeline, 1 ml., was given without effect. Intragastric oxygen was then administered, causing a definite, though temporary, improvement. This was continued for one hour during which the apex beat became gradually weaker, and at the end of this period the child died.

The second twin was delivered 15 minutes after the first, cried well, and did not require any resuscitation. It was subsequently discovered to have a cardiac systolic murmur, although progress to date has been normal.

Necropsy. The body was that of a premature female infant weighing 4 lb. 8 oz. (2·05 kg.). The skin was pink. The only abnormalities were in the respiratory system. The mouth, pharynx and oesophagus were normal. The supraglottic part of the larynx was normal. Immediately below the vocal cords the larynx was completely occluded. This was found to be due to a mass of cartilage 1 cm. thick posteriorly and 0·3 cm. thick anteriorly. The upper surface was convex and the lower concave, forming a dome-shaped covering over the upper end of the trachea (Fig. 1). No communication could be found between the larynx and trachea. The trachea and bronchi contained a large amount of mucus; the lungs were of normal size for a newborn infant. The left lung consisted of one lobe, the right lung of two lobes. The consistency was solid and the cut surface was slimy due to the large amount of mucus in the air passages.

Histological examination of the two lungs showed normal development (Fig. 2); most of the alveolar ducts and alveoli were expanded but there were small areas

FIG. 1.—The larynx opened from behind showing the band of cartilage obstructing the lumen.

of atelectasis. The air passages and alveoli were filled with faintly eosinophilic material which gave the staining reactions for mucin (Fig. 3).

Discussion

Embryology. The development of the larynx is described in detail by Frazer (1910) and more briefly in the *Manual of Embryology* (Baxter, 1953). Only a short summary is needed here. The larynx develops in two parts, the infraglottic as a median sagittal cleft in the floor of the pharynx at the upper end of the pulmonary outgrowth, the supraglottic (transverse part) as a modification of the floor of the pharynx above the sagittal cleft. The vocal cords lie approximately at the boundary between the two parts.

It is the infraglottic part which concerns us now. During the third or fourth week the sagittal cleft is

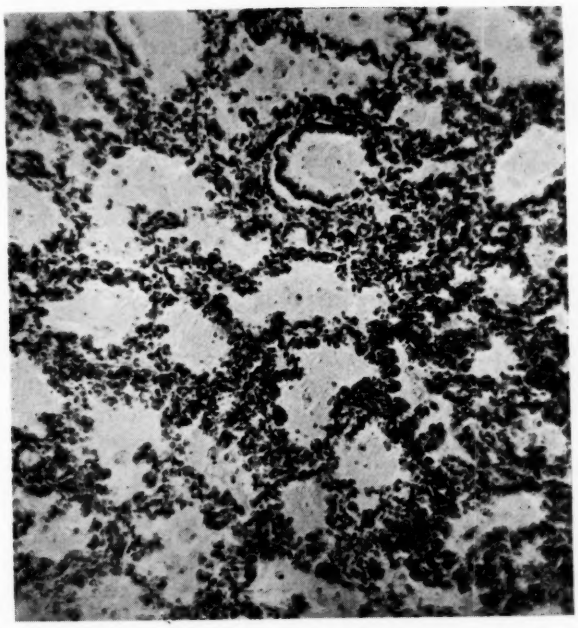

FIG. 2.—Section of lung showing normal development of the alveoli. Haematoxylin and eosin ×225.

almost completely closed by overgrowth of the lateral masses (fifth branchial arches) at the sides. The epithelium fuses, leaving a small channel at the back (ductus pharyngo-trachealis) and sometimes a similar channel anteriorly. With the development of the cricoid cartilages in the lateral masses, the cleft reopens at the eighth-ninth week to form the infraglottic part of the larynx.

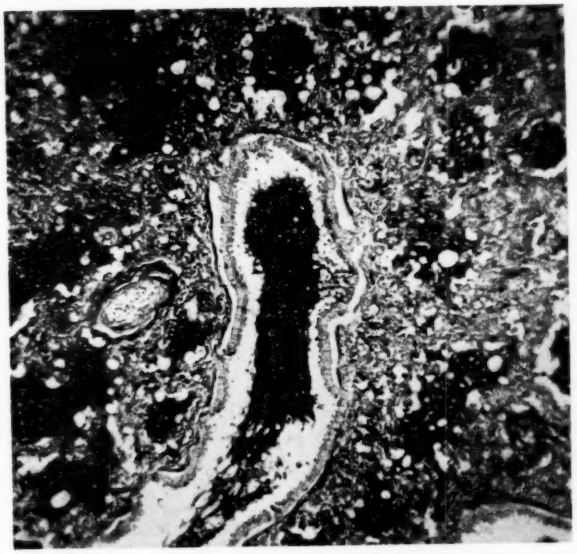

FIG. 3.—Section of lung showing mucus in the air passages and alveoli. P.A.S. ×125.

It is generally agreed that subglottic atresia is due to failure of the sagittal cleft to reopen, usually combined with an overgrowth of cartilage in the lateral masses. The small posterior fistula (ductus pharyngo-trachealis) has been found in many of the reported cases. It was not found in the present case, possibly because the larynx was opened from behind. The development of the lungs was normal in this case and in the others when the lungs are mentioned.

In Bizza's (1941) case the lungs were enlarged and he quotes other cases where this was found. He considered this to be due to retention of mucus. Although the lungs were of normal size in the present case there was considerable retention of mucus (Fig. 3). Snyder and Rosenfeld (1937) produced evidence that a tidal flow of amniotic fluid into the foetal lungs was necessary for their normal development. Potter and Bohlender (1941) denied this, giving a case of laryngeal atresia as an example. They considered that the fluid filling the alveoli and air passages could be transudate. They did not mention the presence of mucus, but noticed 'precipitated protein' in the alveoli histologically. Although it can play no part in the normal development of the lungs, it may be that retained secretions lead to dilatation of the alveoli and so assist the development of the lungs in cases where there is no outlet for the secretion.

Diagnosis. In the absence of any complications at birth which might lead to shock or narcosis, the outstanding symptoms are failure to breathe and cry. The infant is active and makes respiratory movements. Sternal retraction and indrawing of the intercostal spaces, supraclavicular fossae and epigastrium may be seen. The colour is usually normal at birth, but cyanosis soon appears after the cord is tied.

The presence of active movements and attempts at respiration distinguish atresia of the larynx from apnoea due to shock or narcosis, the normal colour at birth from asphyxia and cardiac cyanosis, and the absence of stridor from other laryngeal and tracheal anomalies.

The manoeuvre of clearing the respiratory passages will not help in diagnosis as the catheter seldom enters the larynx. The only certain method is laryngoscopy, which is not easy in a newborn infant. Also facilities for laryngoscopy are not always available at short notice.

Treatment. Without treatment the infant will not survive for many minutes. Potter and Bohlender's (1941) case survived for 20 minutes. The cases of Kessel and Smith (1953) and Sandison (1955) with complete and partial absence of the trachea survived for 66 minutes, and 4 hours 42 minutes. Both had a communication between the oesophagus and air passages and some aeration of the lung was found at necropsy.

Intragastric oxygen can maintain quite adequate oxygenation of the blood in the newborn. Sandison's case was given this treatment for 30 minutes and it produced an improvement in colour. A similar effect was obtained in the present case and survival was prolonged to 60 minutes.

Tracheotomy should be performed as soon as possible after the condition has been diagnosed. The case of membranous atresia reported by Holinger *et al.* (1954) was treated in this way and was alive and well at 10 months. Several other cases in their series were treated by tracheotomy soon after birth with good results. There still remains the danger of respiratory obstruction by the excess of retained mucus in the air passages. There might also be an increased susceptibility to pneumonia.

It has recently been suggested that hyaline membrane represents a highly concentrated secretion from the epithelial cells of the terminal bronchioles and alveolar ducts (Lynch and Mellor, 1955) or endogenous mucus (Wagner, 1954). If these conclusions are correct, an infant with laryngeal atresia and retention of these secretions should be very liable to develop hyaline membrane.

If the infant should survive, it is doubtful whether a satisfactory reconstruction of the larynx would be possible. Even if an airway could be established, permanent aphonia would remain.

Summary

A case of cartilaginous subglottic atresia of the larynx in a twin newborn infant is described. The infant was given intragastric oxygen and survived for 60 minutes. The other twin had no respiratory difficulty but has a cardiac murmur. The embryology, diagnosis and treatment of laryngeal atresia are discussed.

We wish to thank Dr. R. I. Mackay and Dr. G. J. Crawford for permission to publish the case and for their help and encouragement in preparing the text. We are grateful to Miss A. Williams for the histological preparations, Mr. F. G. Warburton for the photographs and Mrs. J. Gregory for clerical assistance.

Addendum

Reconstruction has recently been successfully performed on a child of 2½ years with laryngeal stenosis (Sharp, 1956).

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INTRATHECAL ISONIAZID IN TUBERCULOUS MENINGITIS

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(RECEIVED FOR PUBLICATION APRIL 26, 1956)

The demonstration that isoniazid is inhibitory to the tubercle bacillus (Robitzek, Selikoff and Ornstein, 1951) and possesses potential advantages in the treatment of tuberculous meningitis on account of the freedom with which it diffuses into the cerebrospinal fluid (Fletcher, 1953) has led to its widespread and successful use in this disease. The readiness with which C.S.F. concentrations can be maintained after oral administration has permitted a great reduction in the duration and frequency of intrathecal streptomycin therapy.

Numerous series have now been reported in which results compare favourably with those in which streptomycin alone or in combination with antibiotics other than isoniazid have been used. In several, reliance has been placed on systemic therapy by isoniazid and streptomycin while intrathecal therapy has been virtually withheld (Anderson, Kerr and Landsman, 1953); Bulkeley, 1953; Smellie, 1954; Fitzpatrick, 1954. With such régimes the recovery rates have been higher than any achieved previously without isoniazid so that physicians have shown a justifiable inclination in this country and in America to dispense with intrathecal injections. It is nevertheless realized that to do so in all cases would be therapeutically unsound (Lorber, 1954), and it must be borne in mind that often in these series a short course of intrathecal therapy had been given in the critical early stages. The improved recovery rate has doubtless been assisted by the larger proportion of cases now admitted for treatment at an early stage of the illness. There remain those in which for one reason or another the diagnosis is established only when the disease has reached an advanced stage, and from the nature and variety of the symptoms it is probable that such cases will continue to be seen. Although this group is small it still carries a high mortality rate and incidence of neurological complications, and reveals the limitations of chemotherapy. This study of isoniazid administered intrathecally was undertaken to determine whether any advantages might be gained by intrathecal administration, since the antibiotic's efficiency *in vivo* in respect of bacteriocidal power and ability to penetrate ischaemic tissues depends upon its concentration.

Torres-Gost (1953) has reported encouraging results with this form of treatment but he gives no details of the toxic or side-effects encountered. The present report is concerned primarily with this aspect of intrathecally injected isoniazid and forms a preliminary report on its therapeutic value.

Régime of Treatment

Streptomycin. Streptomycin (20 mg. per lb. of body weight daily) is injected intramuscularly once daily, and, when the infection has been partially controlled, on alternate days. The duration of treatment varies from three to four months or until high frequency deafness is first detectable audiographically.

Streptomycin is injected intrathecally through the same needle at the time of injecting isoniazid, the solutions being made up in separate syringes. Doses range from 25 to 75 mg. of streptomycin according to weight.

Isoniazid. Isoniazid (5-7 mg. per lb. of body weight daily in four doses) is given as 'rimifon' and oral administration is continued throughout treatment in conjunction with streptomycin or P.A.S. It is injected intrathecally, 25-50 mg. according to weight, daily at the start of treatment (Table 1) until improvement as judged by clinical condition and C.S.F. changes becomes apparent. Thereafter injections are given on alternate days and the interval progressively lengthened provided that improvement continues. As confidence in the method was gained the duration was shortened. For injection the drug is dissolved in 2 ml. of sterile distilled pyrogen-free water.

P. Amino-salicylic Acid (P.A.S.). *Para*-amino-salicylic acid (7-18 g. daily in four divided doses according to weight) is given orally to all patients upon discontinuing streptomycin and continued in conjunction with oral isoniazid for several months. Dosage starting at a quarter

TABLE 1
TREATMENT AND COURSE

Case No.	Duration of Daily Intrathecal Injections	Duration of Alternate Daily Intrathecal Injections (Days)	Intrathecal Dosage per lb. Body Weight (mg.)	Relapse	Death	Complications	Sequelae
1	42	—	0·75	+	+	Hydrocephalus	Death
2	35	—	0·75	—	—	—	—
3	49	35	1·25	—	—	—	Hemiplegia
4	21 119	63	1	—	—	—	Quadriplegia, mental defect
5	28	21	1	—	—	—	—
6	28	21	0·5	—	—	—	—
7	10	42	0·3	—	—	Partial optic atrophy	—
8	21	21	0·2	—	—	Convulsion	—
9	21	21	0·75	—	—	—	—
10	14	10	0·3	—	—	—	—
11	1	3	0·5	—	—	—	—
12	8	11	0·4	—	—	—	—
13	7	44	0·3	—	—	—	—
14	10	10	0·5	—	—	—	—
15	21	7	1	—	+	Hemiplegia	—
16	33	5	0·75	—	—	—	—
17	13	13	0·75	—	—	—	—
18	—	21	0·75	—	—	—	—

of the optimal is increased over a period of seven to 14 days according to tolerance to full dosage. By this means intestinal disturbance is minimized and in no case have vomiting and anorexia been sufficiently severe to warrant more than temporary withdrawal or reduction of the dose.

The Patients

All patients suffering from tuberculous meningitis, six adults and 12 children, admitted during the period of the trial have been included (Table 2). Their ages range from 1¼ to 53 years. Bacteriological confirmation of the diagnosis has not been obtained in every case, though in all there was no doubt on clinical grounds, and the cerebrospinal fluids have been cytologically and biochemically typical. Of the 18 patients, six were classed as early, eight as intermediate and four as late.

At the time of diagnosis and the start of treatment, three patients were in coma and six had impaired consciousness of lesser degree. In eight neurological lesions were already present. Two children are included who had relapsed after previous treatment, one following streptomycin therapy only and another after an inadequate course of streptomycin and oral isoniazid.

Isoniazid Levels in C.S.F.

In our earlier patients isoniazid concentrations in the C.S.F. were not measured owing to the lack of a reliable method. Estimations in four later cases were made by the method described by Short (1954). Levels of 1·1, 0·05, 0·45 and 0·3 mg. per ml. were found in C.S.F. 24 hours after intrathecal injection while oral therapy was maintained. In the second of these cases no isoniazid could be detected on two subsequent occasions although the concentration in the serum was 0·13 mg. per ml. In the other cases the C.S.F. levels were of the same order or rather less than those in the blood, so that they are

TABLE 2
CONDITION BEFORE TREATMENT

Name	Case No.	Age	Consciousness	Neurological Complications	Previous Treatment	Stage
D.C.	1	3	Coma	III nerve	+	Late
J.S.	2	2½	Stupor	VI nerve	—	Intermediate
S.H.	3	1	Alert	Hemiplegia	—	Intermediate
C.R.	4	3	Stupor	Quadriplegia hydrocephalus, mental defect	+	Late
J.Mc.	5	2	Drowsy	Miliary	—	Intermediate
T.W.	6	7	Alert	Hemiplegia	—	Intermediate
Y.B.	7	14	Alert	Hemiplegia	+	Intermediate
J.K.	8	18	Coma	—	—	Late
J.M.	9	8	Drowsy	Aphasia VI and VII nerves	—	Intermediate
D.D.	10	24	Stupor	—	—	Intermediate
M.W.	11	26	Alert	—	—	Early
B.W.	12	5	Stupor	Convulsions	—	Intermediate
E.S.	13	9	Alert	—	—	Early
R.F.	14	6	Alert	—	—	Early
G.P.	15	33	Coma	Hemiplegia	—	Late
G.S.	16	53	Drowsy	—	—	Early
J.C.	17	12	Alert	—	—	Early
L.	18	21	Alert	Hemiplegia (Pregnant)	—	Early

probably due to diffusion from the blood and not to intrathecal therapy.

Therapeutic Results

In all patients the infective process has been controlled and only one has died while the cerebrospinal fluid has been still abnormal. One death occurred suddenly in a late case (Case 1) with severe dementia and quadriplegia six months after the end of treatment from secondary hydrocephalus. This child had received intrathecal isoniazid only from the third to the eighth week of the first course of treatment. The second course of treatment, which was instituted at the 18th week on account of relapse, consisted of intrathecal and intramuscular streptomycin and oral isoniazid. At the time of death the C.S.F. contained fewer than 10 lymphocytes, no polymorphs, protein 50 mg. % and sugar 55 mg. %. At necropsy no evidence of tuberculous disease, gross or histological, could be found in the meninges or brain and death is therefore attributed to hydrocephalus occurring as a complication of tuberculous meningitis which itself had healed.

The second death occurred in a marasmic adult aged 33 who was transferred from a mental hospital where he had been a patient on account of schizophrenia. On admission he was in deep coma, with hemiplegia and multiple pressure sores. In spite of combined therapy and cortisone there was no clinical improvement and he died on the 49th day. At that time the cerebrospinal fluid contained sugar, 50 mg. per ml., protein 210 mg. and 24 lymphocytes. At necropsy a small walled-off focus was present over the left hemisphere but no evidence of active meningitis. There was gross cerebral softening.

In Case 4, the situation is similar in that the infection has been controlled, but there is residual hydrocephalus, dementia and quadriplegia. This child had been treated previously with streptomycin only and at that time the neurological lesions had appeared. They were present when intrathecal isoniazid was begun at the time of her relapse, and, although this has been controlled, the cerebral damage has shown no improvement.

In no patient have complications appeared after the start of treatment and in all others recovery has been complete, apart from pre-existing neurological lesions. Pre-existing neurological lesions underwent some improvement during and after treatment as judged by clinical examination, and in only one besides that already mentioned has there been any significant disability. In no instance was there exacerbation that might be attributed to focal oedema (Ritchie, Taylor and Dick (1953).

A minor degree of optic atrophy with minimal constriction of the visual fields developed in Case 7 which had previously relapsed.

Side-effects

Central Stimulation. Two major epileptic seizures in close succession occurred in Case 8 (an adult) in the eighth week of treatment. This man had suffered from convulsions in infancy, and the E.E.G. revealed a mild paroxysmal instability. Apart from some restlessness there were no other effects attributable to isoniazid, and since continued treatment did not provoke further convulsions, it is probable that isoniazid was at the most only a minor factor in its causation.

No other phenomena attributable to isoniazid toxicity on the central nervous system as described by Castle, Carr, Chamberlain, D'Esopo, O'Connor, Pfuetze, Tucker, Tempel and Ebert (1953) were encountered.

Meningeal Irritation. In two patients (Cases 3, 7) there were findings in the C.S.F. consistent with low-grade chemical meningitis. In both the C.S.F. protein steadily increased to 350 mg. and 800 mg. respectively, which diminished on withholding treatment.

The C.S.F. of the first patient also showed a pleocytosis (350 polymorphs per ml.) during treatment, which disappeared rapidly on withdrawal. The second patient at the time of the rise of C.S.F. protein developed a partial spinal block which resolved slowly but completely following withdrawal of intrathecal therapy. The long duration of the disease and its relapse could alone have caused the C.S.F. changes in this patient, and it is unlikely that isoniazid had any significant effect. In neither case did these reactions cause any permanent sequelae. While present there were mild symptoms of meningeal irritation, namely headache and occasional vomiting with poor appetite, which, though not severe enough in themselves to warrant stopping treatment, were unpleasant. In the first patient (Case 3), the youngest in the series, the dosage was by weight the highest (1·25 mg./lb.) and was perhaps more than was necessary. Our impression is that the severity of the meningeal reaction is comparable to that caused by streptomycin or penicillin when administered intrathecally.

Discussion

The reason for investigating the value of injecting isoniazid intrathecally when the present inclination is to reduce intrathecal treatment lies in the unfavourable results still encountered in advanced

disease and the desirability of bringing about further improvement.

Failures may be broadly divided into those cases which die before treatment can become effective, those in which permanent brain damage occurs and those which relapse through inability to eradicate the infection. While all are directly related to delay in instituting effective therapy, it is possible that even in such late cases a more rapid and complete antibacterial effect might prevent a proportion of these failures, and also permit some reduction in the duration of treatment.

The importance of rapid bacteriostasis in the prevention of early deaths is obvious. In preventing relapses it is likewise important, since the work of several investigators has clearly shown (Ritchie, Taylor and Dick, 1953; Dick, 1953 and 1954) that early lesions can undergo complete resolution and sterilization under the influence of chemotherapy whereas late foci merely become walled off and are not sterilized (Hobby, Lenert, Rivoire, Donikian and Pikula, 1953). In this connexion isoniazid possesses manifest advantages over streptomycin as less fibrosis occurs and more complete healing is allowed (Hobby *et al.*, 1953), and is therefore an indispensable drug in any therapeutic régime.

It is thus necessary to determine whether there is room for greater efficiency in the use of available antibiotics. In practice this may be reduced to consideration first of the optimal therapeutic concentration and secondly of its attainment in the tuberculous focus. In the first place Lecocq and Linz (1952) have shown that a large number of microorganisms raise the minimal concentration of isoniazid necessary for inhibition, so that there may be need for higher minimal concentrations of isoniazid in late rather than in early disease. The question of whether concentrations of isoniazid which exceed the minimal offer any therapeutic advantage by possessing greater antibacterial activity has been studied by Fletcher (1953) and Barclay, Ebert and Koch-Weser (1953). They found little evidence to suggest that increasing the concentration increased inhibitory activity. Later, however, Singh and Mitchison (1954) found convincing evidence that the antibacterial effect is in fact enhanced. Furthermore the laboratory finding that isoniazid in high concentration reduces the viability not only of actively growing bacteria but also of resting organisms (Peizer, Widelock and Klein, 1954) must be considered as a potential therapeutic advantage.

As the tuberculocidal action of isoniazid is enhanced quantitatively and qualitatively by increasing its concentration, in practice a greater antibacterial effect would be expected and must be exploited by ensuring that the dosage and route of administration enable such concentrations to reach the microorganism,

The second point, namely the attainment of optimal levels at the site of infection, may under favourable conditions be satisfied by increasing the oral dosage. In tuberculous meningitis there are, however, special features which not infrequently interfere with free access.

Isoniazid diffuses from the blood stream to the C.S.F. with little fall in concentration (Fletcher, 1953), and inhibitory concentrations can be maintained in the C.S.F. after oral administration. In early cases there is probably no significant obstruction to the free flow of C.S.F. and the passage of the drug to the site of infection is unimpeded. On the other hand in late disease, exudate, which is insufficient to cause gross obstruction, may obstruct the capillary spaces of the sulci at whose bases lie the tuberculous foci and prevent free circulation of the drug. In these circumstances it may not be possible to bring adequate concentrations of drugs, such as streptomycin, which depend on free circulation of C.S.F., into contact with the organism.

With isoniazid, on the other hand, the only theoretical difficulty in obtaining optimal therapeutic local concentrations arises when the tuberculous focus is deeply buried in brain tissue and the blood supply is also impaired. In chronic lesions the zone of endarteritis and ischaemia which surrounds the focus may form a barrier to blood-borne agents. High concentrations may then only be obtainable by providing such high levels in the C.S.F. or blood that a small amount will permeate the ischaemic brain tissue to reach the site of infection. In normal brain the concentrations reached are probably lower than those in the blood, since Barclay, Ebert, Le Roy, Manthei and Roth (1953) have demonstrated that the concentrations in less vascular structures such as fat and bone are about one-half those in the blood. While they performed no estimations on brain tissue it is probable by analogy with the behaviour of other antibiotics than those of isoniazid are also low.

The state of a tuberculous focus itself appears to matter little; concentrations of isoniazid of the same order as those bathing the surface are rapidly obtained in its depths irrespective of the extent of fibrosis and exudate or the amount of caseous material (Barclay *et al.*, 1953). Similarly isoniazid diffuses freely into the macrophage reaching a concentration similar to that outside the cell (Mackaness and Smith, 1952; Suter, 1952). In this respect it differs from streptomycin which virtually

fails to enter the cell and thus has little effect on intracellular microorganisms.

The therapeutic problem in advanced tuberculous meningitis is therefore seen to be caused as much by the changes in the surrounding tissues and blood vessels which hinder diffusion of antibiotic agents as by the character and size of the focus. In view of the potential advantages of concentrations of isoniazid which are higher than those generally accepted as sufficient and of the manifest difficulties in obtaining them at the tuberculous focus itself, as distinct from the body fluids, there is a strong argument in support of intensive therapy by combined local and systemic administration. Intrathecal administration of isoniazid with streptomycin in addition to high parenteral dosage provides means of ensuring optimal local concentrations. Toxic effects prohibit any increase in the parenteral dose of streptomycin and to a less extent of isoniazid, though with the latter a higher oral dosage, than is routinely employed e.g., 7-10 mg. per lb. body weight per day, has been used with apparent safety.

Intrathecal injection of isoniazid in the dosage employed has been shown in the present trial to be a safe procedure and reasonably free from side-effects due to non-specific irritation of the meninges. In our experience intrathecal dosage on the scale of 0·5 mg. per lb. of body weight is satisfactory both in respect of therapeutic efficiency and freedom from side-effects. While no detectable ill-effects occurred with a dosage of 1 mg. per lb., mild irritation was probably caused by a dosage of 1·25 mg. per lb. in one case and it is felt that 1 mg. per lb. may leave insufficient margin of safety. In the low-dosage range we gained the impression that the response to treatment was relatively slow with a dosage of 0·3 mg. per lb. or less.

Although estimations of the isoniazid concentration in the C.S.F. were made they do not indicate the highest levels obtained and for the reasons already given are of little value as a guide to the concentration in the tuberculous focus itself. The therapeutic response is considered to be the surest means of determining whether the local concentration is optimal.

Summary

The treatment of 18 patients suffering from tuberculous meningitis with intrathecal isoniazid is described.

In 17 cases the infection was eradicated. There were two deaths.

The side-effects of intrathecal isoniazid were few. In one infant on high dosage there was evidence of non-specific meningeal irritation which disappeared on withdrawal. In an adult with an abnormal electroencephalogram and a history of previous convulsions, two major epileptic attacks occurred, but treatment was continued.

The importance of rapid control of the infection and the therapeutic value of high local concentrations of isoniazid at the start of treatment are discussed.

I wish to thank Dr. S. R. M. Bushby of the Wellcome Physiological Research Laboratories for performing the isoniazid estimations, and Dr. J. S. Norell for his assistance in the early stages of the work.

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BOOK REVIEWS

The Boke of Chyldren. By THOMAS PHAIRE. Edited by A. V. Neale and Hugh R. E. Wallis. (7s. 6d.) Edinburgh: E. & S. Livingstone. 1955.

Not to know of Thomas Phaire (as I did not) is to proclaim one's ignorance, but, by the same token, to declare one's gratitude to A. V. Neale and Hugh Wallis for this tardy introduction to him. Guthrie in *A History of Medicine* has a paragraph on Thomas Phaer, or Phayre, for Phaire, like Shakespeare, spelt his name according to his daily whim. Thomas Phaire was born in Norwich about the year 1510, 125 years before Thomas Browne settled there in practice and 154 years before Shakespeare was born. He lived at Kilgerran in Pembrokeshire and there died in 1560. He began to practise medicine at the age of 28, having previously studied law at Oxford and Lincoln's Inn. His book, which Neale and Wallis have edited, is the first English textbook on the diseases of children. It was published in 1545 as an addition to *The Regiment of Life* which Phaire had translated from a French version of *Regimen Sanitatis Salerni*. Guthrie quotes Aikin (1700) as stating that *The Boke of Chyldren* was also translated from the French. This is an error which is sufficiently obvious from Phaire's preface to the book, although our editors do not contradict it. The book is Phaire's alone and its Englishness is everywhere apparent. The transcript is made from the 1553 edition, a copy of which is in the Medical Library of the University of Bristol—a book of 56 pages. The editors have retained both the antique spelling and the printing, except for the substitution of the modern 's', which makes for easier reading. In his preface Phayre states his purpose: 'to doo theym good that have moste nede, that is to saye, children'. The rest of the preface is occupied with a defence of the distribution of such works in English, 'to them that are unlearned'; we can judge how far Phaire was before his time when we recall that Heberden, *ultimus Romanorum*, more than 200 years later, thought that all medical treatises should be written in Latin. The editors have removed all labour from our pleasure by providing an erudite glossary and materia medica. How many readers will know, or can guess, the modern English for 'kybes', 'pushes', 'yeaxing', 'seege' and 'cony'?

All paediatricians should read this little book for the acuteness of its observation, the charm of its old English, its physicianly sympathy for the helpless and the knowledge which it provides of the diseases of children 400 years ago. One quotation only, from this most quotable of books, must suffice: 'the best and moste sure helpe in this case (smal pockes and measilles) is not to meddle with anye kynde of medicines, but to let nature worke her operaciō'.

Year Book of Pediatrics. Series 1955/56. Edited by SIDNEY S. GELLIS and ISAAC A. ABT. (Pp. 431; 112 figures. 45s.) Chicago: The Year Book Publishers; distributed in Great Britain by Interscience Publishers. 1955.

This year's *Year Book of Pediatrics* is rather less parochial than most of its forerunners, more than a third of its abstracts dealing with the non-American literature. The result is that the reader obtains a far more comprehensive picture of what is going on in paediatrics.

The book follows the usual pattern, with abstracts of varying lengths frequently being followed by comments from selected critics. The Editor acknowledges in his preface that this sort of one-way correspondence column is unsatisfactory to the author of a reviewed article who is unable to defend himself from what sometimes seems to be carping criticism, but it is clear that a book appearing once a year cannot publish an interchange of correspondence. Whether or not the valuable and well-selected abstracts which the *Year Book of Pediatrics* brings before us would be better left uncluttered by comment is a matter of sharply divided opinion, but if A is to be allowed to have an unanswered fling at B in one year it would be equitable if B were allowed similarly to criticize something of A's in the following year. As paediatricians, one of our duties is to convince the young of the essential unfairness of life, and we could well cite the practice of the *Year Book of Pediatrics* in our support.

Premature Infants, 2nd ed. By ETHEL C. DUNHAM. (Pp. xiii+459; 41 figures, 76 tables. 63s.) London: Cassell. 1956.

This nice book is divided into general considerations, clinical considerations and public health considerations, and includes an appendix of various tables and methods of measurement. The book is written with a proper regard to the increasing importance of prematurity as a cause of neonatal death and morbidity and much has been assembled that will be of interest to the family doctor as well as to the paediatrician.

The general and public health considerations deal essentially with the premature infant, but nearly 200 pages of the clinical section have little bearing on the premature infant particularly, and are better covered in the standard paediatric textbooks. The appendix contains a whole mass of useful information on many unexpectedly interesting facets of the care of premature infants and is well worthy of study.

The book is elegantly produced and for 63s. could scarcely be improved on.

Modern Methods of Feeding in Infancy and Childhood, 10th ed. By DONALD PATERSON and GEORGE NEWNS. (Pp. ix+188; illustrated. 15s.) London: Constable. 1956.

It is usually said that textbooks are at least five years behind the most recent advances in any subject. This book remedies that situation as far as infant feeding is concerned. It is a clear, concise account of the present-day ideas on the subject, and gives precise instructions, advocating the more liberal feeding advised to-day. If amongst doctors and nurses there are still some who fear overfeeding, or worry about slight variations in composition, this book will help to remove their doubts. It will support mothers who, I suspect, often felt that the rigid schedules of the past were wrong.

It contains a wealth of factual information mainly in the form of tables, and reflects the mature opinion of two experienced and widely read clinicians, retaining only those ideas of the past which have stood the test of time, without advocating doctrines not yet fully accepted. It discusses difficulties likely to be met and their management. One or two subjects perhaps might have been more fully discussed, such as 'rooming-in' and 'demand feeding', and a minor criticism of the later chapters on such subjects as prematurity, diarrhoea, vomiting and constipation is that they are perhaps not detailed enough for doctors, yet too detailed for mothers. These, however, form a comparatively minor section of this excellent book which has some valuable diets and suggestions for feeding infants and children suffering from conditions requiring special food such as coeliac disease, obesity, etc. The book is well indexed and the numerous references are listed and because of its style is likely to have a wide appeal. It should be read by all who are concerned with infant feeding and it should find a place in the library of every hospital, welfare clinic and doctor, especially at the reasonable price at which it is published.

Congenital Syphilis: A Follow-up Study with Reference to Mental Abnormalities. By BERTIL HALLGREN and EINAR HOLLSTROM. *Acta psychiatrica et neurologica scandinavica*, Supplementum 93. Copenhagen: Munksgaard. 1954.

The authors present a detailed account of their attempt to estimate the incidence of mental abnormalities in 500 children with congenital syphilis admitted to 'The Little Home' in Stockholm since December, 1900.

Their findings confirm those of previous workers in demonstrating that there is an abnormally high incidence of mental deficiency, mental subnormality and behaviour disorders in these subjects; that these abnormalities are more frequently due to environmental and hereditary factors than to syphilis; but that in some cases syphilitic involvement of the nervous system is directly responsible for mental deficiency.

The material is carefully considered and although the difficulties inherent in this type of investigation militate against clear-cut results, there is much that is of interest in this monograph.

Lehrbuch der Tuberkulose des Kindes und des Jugendlichen. 2nd ed. By WEINER CARTEL. (Pp. xxiv+501; 148 figures. DM. 66.-.) Stuttgart: Georg Thieme Verlag. 1954.

This textbook of tuberculosis in childhood sets out to cover every aspect of the disease and, in very large measure, succeeds in its endeavour. In eight sections containing 30 chapters and almost 500 pages the subject is dealt with systematic thoroughness and a vast wealth of detail. Sections are so arranged that each broad aspect of the disease is separately considered, so that whilst section 2 deals with the primary complex and its complications, section 4 with widespread tubercle and section 5 with the tertiary phase, differential diagnosis in section 6 and treatment in section 8, each deal with all forms of the disease. This type of arrangement gives the book an academic, at times unrealistic, flavour, perhaps unavoidable, which is the sacrifice which has been paid for the sake of quality and comprehensive detail.

The author's passion for the latter is illustrated by his paragraphs on the influence on tuberculosis exerted by the weather and by nutrition, to take two examples. He becomes involved in rather facile expositions of the biological value of the structure of proteins on the one hand, and on the other of the structure of cold and warm fronts. These criticisms are minor ones only, and are more than offset by the massive erudition that makes this book invaluable as a reference and teaching manual.

A major omission, and a more important criticism, is the absence of any section or chapter on the social aspects of tuberculosis. Only here and there in the text are there occasional comments and figures indicating that the author is concerned with the impact that the disease makes on the community, on its cost in ill-health and unhappiness as well as in lives, and perhaps above all on the changing pattern of the disease under the impact of improved social conditions, antibiotics and active immunization.

This second volume has been largely rewritten, and is luxuriously produced, profusely illustrated, clearly printed in easy German, contains many references at the end of each chapter and there is a reasonable index.

Paediatrics—Supplement, 1956. Edited by W. GAISFORD and R. LIGHTWOOD. (Pp. v+115+Index; 19 figures. 32s. 6d.; £14 10s. complete work.) London: Butterworth. 1956.

When *Paediatrics for the Practitioner* appeared we were promised that we would be kept up to date with advances in children's medicine, and this present volume keeps that editorial promise. The volume contains an article on the physical changes of puberty by Lorimer Dodds and a monograph by A. W. Woodruff on the care of children in the tropics. There are also 18 pages called 'Noter-up'. This not very elegant word after due research was found to denote in fewer letters a 'bringer-up-to-dater'. Much useful information on such subjects as lead poisoning, leukaemia and the antibiotics are contained in this section. To use the book properly now the subject should be read in the main volumes and the 'Noter-up' consulted for any really recent advances. This first supplement of *Paediatrics* concludes with 10 more pages of index.